CRITICAL CARE MEDICINE
Vol. 20, No. 6
Printed in U.S.A.

Case Reports

Therapeutic use of omeprazole for refractory stress-induced gastric mucosal hemorrhage

PHILIP S. BARIE, MD, FCCM; ROBERT J. HARIRI, MD, PHD

With the aggressive use of effective prophylactic measures, stress-induced gastric mucosal hemorrhage is unusual but has not been completely eliminated (1). In the setting of critical illness and multiorgan failure, established hemorrhage may be difficult to control. Uncontrollable hemorrhage may require emergency surgery, with a high attendant mortality rate (2). We report a case of successful control of stress-related gastric mucosal hemorrhage, in the setting of a multifactorial coagulopathy, by the administration of omeprazole.

CASE REPORT

A 28-yr-old male with end-stage renal disease, secondary to glomerulonephritis, received a cadaver renal transplant. Twelve years previously, he had undergone total abdominal colectomy with ileoanal anastomosis for ulcerative colitis. An episode of acute rejection was successfully treated with "pulse" prednisone, and the patient was discharged on cyclosporin A, prednisone, ranitidine, and nifedipine.

The patient was readmitted 62 days after transplantation with hematochezia, abdominal distention, and marked tenderness on rectal examination. Proctosigmoidoscopy demonstrated hemorrhage from an ileal perforation at the anastomosis, consistent with a cytomegalovirus enteritis. Creation of an end-ileostomy with packing and drainage stabilized the patient. "Stress-dose" prednisone was administered.

The patient's immediate postoperative course was stormy, with immediate oliguria and azotemia unresponsive to fluid administration, renal-dose dopamine, and diuretics administered with the advantage of information derived from the use of a pulmonary artery catheter. Marked hypoxemia and pulmonary infiltrates eventually led to the need for endotracheal reintubation on postoperative day 6. On that day, cytomegalovirus pneumonitis was confirmed by bronchoalveolar lavage, and blood cultures grew *Enterococcus faecium*. Therapy included vancomycin, ganciclovir, cytomegalovirus immunoglobulin, prophylactic antacids to maintain gastric pH >5.0, total parenteral nutrition, hemodialysis, and discontinuation of cyclosporin A.

On postoperative day 11, the patient became jaundiced, developed abdominal tenderness and serosanguinous wound drainage, and passed a small amount of bright-red blood via the nasogastric tube. He underwent repair of a fascial dehiscence; there was no intra-abdominal infection noted at laparotomy. Over the next week, the patient bled persistently from his stomach. Gastroscopy confirmed the diagnosis of gastritis. A coagulogram was consistent with the diagnosis of disseminated intravascular coagulation. Antacid therapy maintained control of gastric pH, which was ≥5.0 on 32/34 determinations over 7 days, and was never <4.5. Uremic thrombocytopathy was treated with hemodialysis, cryoprecipitate, arginine vasopressin, conjugated estrogens, and platelet transfusions. Fresh frozen plasma maintained the prothrombin and activated partial thromboplastin times within normal limits, despite rapidly deepening jaundice. However, none of these measures arrested the gastric hemorrhage, which resulted in the need to transfuse the patient with 19 units of packed RBCs over a 7-day period (Fig. 1).

On postoperative day 18, 20 mg of omeprazole (every 12 hrs) was begun via the nasogastric tube. Gastric hemorrhage diminished within 12 hrs and ceased within 24 hrs; only 3 units of packed RBCs was transfused over the subsequent 7 days. The total volume of gastric secretions aspirated via the nasogastric tube decreased from a mean of 1362 mL/24 hrs to 391 mL/24 hrs; enteral feedings were tolerated on day 5 of omeprazole therapy. Despite successful control of gastric hemorrhage and full supportive measures, the patient suffered a *Candida parapsilosis* fungemia on postoperative day 25, progressive renal, hepatic, and respiratory failure, and died on postoperative day 41.

DISCUSSION

Persistent, refractory gastric mucosal hemorrhage can be multifactorial in etiology in the critically ill patient. In this circumstance, sepsis with disseminated

From the Department of Surgery, Cornell University Medical College, New York Hospital-Cornell Medical Center, New York, NY.
Address requests for reprints to: Philip S. Barie, MD, Department of Surgery, F-2008, New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, NY 10021.
Key Words: omeprazole; upper gastrointestinal hemorrhage; gastritis; multiorgan failure; sepsis; disseminated intravascular coagulation; critical care
0090-3493/92/2006-0899$03.00/0

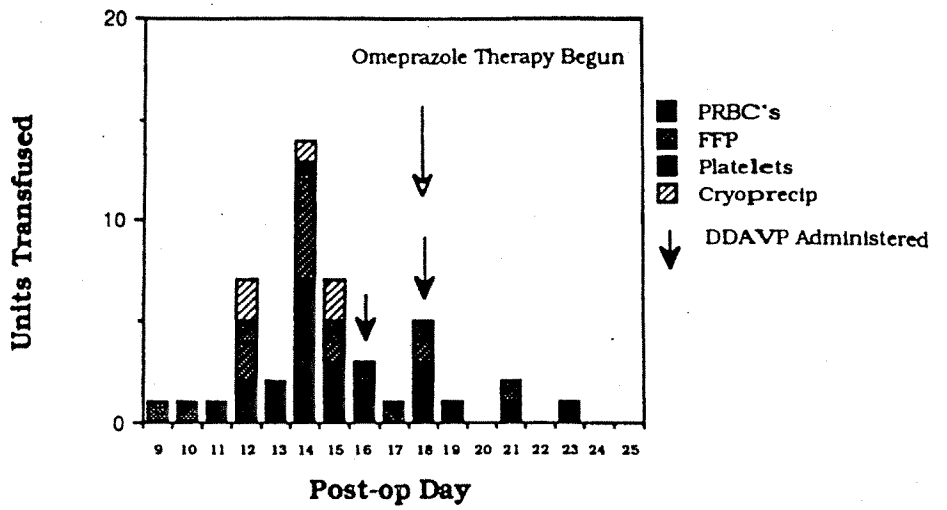


Figure 1. Transfusion requirements for the patient, which decreased markedly after omeprazole therapy. For purposes of clarity, 1 unit of platelets represents a 6-unit platelet transfusion. Similarly, 1 unit of cryoprecipitate represents transfusion of 10 units of cryoprecipitate; for example, the patient received 20 units of cryoprecipitate on postoperative day 12. *PRBC's*, packed red blood cells; *FFP*, fresh-frozen plasma; *cryoprecip*, cryoprecipitate; *DDAVP*, synthetic arginine vasopressin.

intravascular coagulation, hepatic failure with impaired synthesis of coagulation factors, and acute renal failure with uremic thrombocytopathy combined to produce a complex coagulopathy that made the gastric hemorrhage very difficult to control. Massive transfusions of blood and blood products matched ongoing losses, but aggressive measures to correct the coagulopathy, including the administration of cryoprecipitate, arginine vasopressin, and conjugated estrogens to reverse the platelet dysfunction of uremia, did not stop the hemorrhage. Parenteral histamine-2-receptor antagonists were considered contraindicated in view of ongoing thrombocytopenia, and gastric pH was increased to an ostensibly suitable degree with the use of antacids regardless.

Omeprazole, which rapidly and completely controlled the gastric hemorrhage in this patient, is a potent inhibitor of gastric acid secretion. Omeprazole acts by an irreversible inhibition of the hydrogen-potassium adenosinetriphosphatase enzyme, which regulates hydrogen secretion in exchange for intraluminal potassium via an active transport mechanism. Suppression of gastric acid secretion begins within 1 hr of a single dose of omeprazole and is maximal within 2 hrs. With daily use for ≥1 wk, acid secretion is 97% suppressed by a 30-mg daily dose, and persists for 3 to 5 days after cessation of therapy (3).

Data are limited with respect to the use of omeprazole for gastrointestinal bleeding in the setting of critical illness. Omeprazole is effective for prophylaxis of stress-related gastric mucosal hemorrhage in rat models of submersion (4) or transection of the cervical spinal cord (5). However, data regarding therapeutic use in humans to stop active bleeding are limited. Upper gastrointestinal hemorrhage, secondary to Zollinger-Ellison syndrome (6) and reflux esophagitis (7), has been interrupted with omeprazole, but therapeutic use for stress-related hemorrhage is limited to a single report (8).

Omeprazole therapy is associated with few short-term side-effects in noncritically ill patients, but data are lacking in the ICU. Headache, diarrhea, and nausea have been reported in the former group. Of greater concern may be the possible association between suppression of gastric acid secretion and development of nosocomial pneumonia (9), a serious complication of critical illness.

High-dose sucralfate has also been reported to stop refractory stress-related bleeding (10). However, sucralfate requires the presence of acid within the stomach for polymerization and adherence, and may not be rapidly effective in the immediate aftermath of aggressive gastric pH control. Surgery may be required if all measures fail to control hemorrhage. However, this patient population is at high risk for surgery caused by underlying critical illness. An operative mortality rate of 54% was reported in the most recent large series (9). No operation other than total gastrectomy, which

carries the greatest morbidity and mortality rates, has reliably demonstrated effective control of stress-related gastric hemorrhage. Postoperative rebleeding occurs in ≥25% of operated patients who undergo less than a total gastrectomy, and directly causes death in as many as 20% of patients who bleed (10). Effective pharmacologic modalities for secure control of refractory gastric mucosal hemorrhage should be avidly sought.

REFERENCES

1. Reines HD: Stress ulcer—Gone the way of polio and smallpox? *In:* Critical Care: State of the Art. Lumb PD, Shoemaker WC (Eds). Fullerton, CA, Society of Critical Care Medicine, 1990, pp 259–270
2. Humbert JP, Kiernan PD, Welsch JS, et al: The surgical management of bleeding stress ulcers. *Ann Surg* 1980; 191:672–676
3. Olbe L, Verlind T, Elander B, et al: Properties of a new class of gastric inhibitors. *Scand J Gastroenterol* 1979; 55:S131–132
4. Yamamoto O, Okada Y, Okabe S: Effects of a proton pump inhibitor, omeprazole, on gastric secretion and gastric and duodenal ulcers or erosions in rats. *Dig Dis Sci* 1984; 29:394–401
5. MacLellan GD, Shulkes A, Hardy KJ: Effect of omeprazole on acute gastric stress ulceration in cervical cord transected rats. *Dig Dis Sci* 1987; 32:417–421
6. Vezzadini P, Tomassetti P, Marrano D, et al: Life–threatening gastrointestinal hemorrhage with omeprazole. *Dig Dis Sci* 1988; 33:766–767
7. Hetzel DJ, Bonnin M: Long term management of hemorrhagic esophagitis with cimetidine and omeprazole. *Aust N Z J Med* 1986; 16:226–228
8. Collier DStJ, Campion J, Everett WG: Acute haemorrhagic gastritis controlled by omeprazole. *Lancet* 1989; i:776
9. Driks MR, Craven DE, Cell BR, et al: Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. *N Engl J Med* 1987; 317:1376–1382
10. Tryba M, May B: Acute treatment of severe hemorrhagic gastritis with high-dose sucralfate. *Lancet* 1988; ii:1304

Hemodynamic confirmation of septic shock in disseminated tuberculosis

SEEMA S. AHUJA, MD; SUNIL K. AHUJA, MD; KENNETH R. PHELPS, MD; WILLIAM THELMO, MD; A. ROSS HILL, MD

Circulatory disturbances that are characteristic of septic shock are known to result from Gram-negative, Gram-positive, anaerobic, and fungal infections (1). A syndrome reminiscent of septic shock, "sepsis tuberculosis gravissima," has been attributed to disseminated tuberculosis (2, 3), but hemodynamic characterization of this syndrome has been limited to two reports (4, 5) from France. We describe two patients in whom disseminated tuberculosis was the only demonstrable cause of hemodynamically confirmed septic shock, adult respiratory distress syndrome (ARDS), and multisystem organ failure.

From the Departments of Medicine and Pathology, Kings County Hospital Center, and SUNY Health Science Center at Brooklyn, Brooklyn, Brooklyn, NY.

Present affiliations: National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Seema Ahuja), National Institutes of Health (NIH); National Institute of Allergy and Infectious Diseases (Dr. Sunil Ahuja), NIH, Bethesda, MD; Department of Medicine (Dr. Phelps), Albany Medical College, Albany, NY; Department of Pathology (Dr. Thelmo), Kings County Hospital Center, Brooklyn, NY; Department of Medicine (Dr. Hill), SUNY Health Science Center at Brooklyn, Brooklyn, NY.

This study was supported, in part, by the Department of Medicine, SUNY Health Science Center at Brooklyn, Brooklyn, NY.

Address requests for reprints to: Seema Ahuja, MD, NIDDK, Bldg. 10, Room 3N114, National Institutes of Health, Bethesda, MD 20892.

Key Words: sepsis; septic shock; tuberculosis; hemodynamics; adult respiratory distress syndrome; multiple organ failure; blood gas analysis; vasopressors; AIDS-related complex

CASE REPORTS

Patient 1. A 34-yr-old black male presented with a 3-wk history of fever, cough, and weight loss. He denied iv drug abuse, homosexual contact, or heterosexual promiscuity. There was a questionable history of alcoholism. Respiratory rate was 30 breaths/min, heart rate 140 beats/min, BP 100/60 mm Hg, and temperature was 40°C. Coarse rales were evident over both lung fields. The heart, abdomen, and nervous system were unremarkable. A chest roentgenogram showed diffuse bilateral alveolar infiltrates. Arterial blood gases obtained while the patient breathed room air were pH 7.42, $Paco_2$ 22 torr (2.9 kPa), and Pao_2 46 torr (6.1 kPa).

Treatment for possible *Pneumocystis carinii* pneumonia or bacterial pneumonia was initiated with iv trimethoprim-sulfamethoxazole, oxacillin, and ceftriaxone. Laboratory data suggested disseminated intravascular coagulation and acute renal failure (Table 1). Sputum examination was noncontributory. Mechanical ventilation was instituted because of refractory hypoxemia. On day 2, BP decreased to 60/40 mm Hg and was unresponsive to fluid administration. Data derived from pulmonary artery catheterization showed a high cardiac output and low systemic vascular resistance

Vol. 49 April 1960 No. 4

SCIENTIFIC EDITION

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

1852 A.Ph.A. 1960 SECOND CENTURY

CONTENTS OF THIS ISSUE

An Evaluation of Certain Hypotensive Agents III. Tetrahydroisoquinoline and Tetrahydroquinoline Derivatives 183
R. K. Bickerton, M. L. Jacquart, W. J. Kinnard, Jr., J. A. Bianculli, and *J. P. Buckley*

The Alkaloids of *Argemone munita* subsp. *rotundata* 187
Lemont B. Kier and *Taito O. Soine*

Preparation and Properties of New Gastric Antacids I. Aluminum Hydroxide-Magnesium Carbonate Dried Gels 191
Stewart M. Beekman

Preparation and Properties of New Gastric Antacids II. Aluminum Hydroxide-Protein Dried Gels 201
Stewart M. Beekman and *Carl H. Vogel*

The Effects of Certain Psychopharmacologic Drugs on Conditioning in the Rat I. Avoidance-Escape Conditioning 205
V. D. Lynch, M. D. Aceto, and *R. K. Thoms*

The Antidotal Effectiveness of Sodium Cobaltinitrite in Antagonizing Cyanide Poisoning in Albino Mice 210
Marvin M. Goldenberg and *David E. Mann, Jr.*

A Comprehensive Pharmaceutical Stability Testing Laboratory III.. A Light Stability Cabinet for Evaluating the Photosensitivity of Pharmaceuticals 213
Leon Lachman, Charles J. Swartz, and *Jack Cooper*

A Preliminary Pharmacologic Investigation of the Roots of *Bixa orellana* 218
Norris W. Dunham and *Kenton R. Allard*

An Investigation of Some Pharmaceutical Applications of Certain Fatty Acid Esters of Sucrose 220
Howard Hopkins and *LaVerne D. Small*

[illegible] Tranquilizers on Bacterial Toxemias I. Reserpine 225
[illegible]*rg, James W. Ingalls,* and *Arthur G. Zupko*

[illegible]ugs by Plastics II. Interaction of Weak Organic Acids with Plastic Syringes 227
[illegible] and *J. Autian*

[illegible]e Inhibitory Effect of Combined Chemical Preservatives on *Saccharomyces cerevisiae* 231
[illegible]*an* and *Afaf El-Mariah*

Influence of Hydrophil-Lipophil Balance on Ointment Bases 234
John W. Rhyne, William J. Payne, and *Charles W. Hartman*

The Interaction of Citrate With Aspirin and Benzoic Acid 237
Sanford Bolton

Veratrum Alkaloids XLIII. The Structure of Cevadine 242
S. Morris Kupchan and *Adriano Afonso*

Some Pharmaceutical Properties of Novobiocin 245
John D. Mullins and *Thomas J. Macek*

The Effect of Thixotropy on Suspension Stability 249
Ernest C. Foernzler, Alfred N. Martin, and *Gilbert S. Banker*

A Note on the Photolytic Degradation of Anti-inflammatory Steroids 253
W. E. Hamlin, T. Chulski, R. H. Johnson, and *J. G. Wagner*

A Note on an Infrared Assay of Chloroform in Pharmaceutical Products 255
John C. Souder and *Patrick Deluca*

A Note on the Occurrence of 2,6-Dimethoxybenzoquinone in *Rauwolfia vomitoria* 257
S. Morris Kupchan and *Mang E. Obasi*

Book Notices 258

Advertising ..... Cover pages 2, 3, and 4, and I to IV

Preparation and Properties of New Gastric Antacids I*

Aluminum Hydroxide–Magnesium Carbonate Dried Gels

By STEWART M. BEEKMAN

The preparation and properties of two new, highly reactive aluminum hydroxide–magnesium carbonate dried gels (AHMC) are described. The rate of reaction with gastric acid is shown to be rapid as well as prolonged in the optimum pH range of 3 to 5. Three methods were used to determine reaction rate including the Reheis and Mutch reaction velocity tests as well as a modified procedure of Holbert, Noble, and Grote. An automated apparatus for antacid evaluation is described. Data on thirteen antacid chemicals as well as thirty of the most widely used antacids in liquid and tablet form are presented. The *in vitro* antacid properties of AHMC dried gels compares favorably with reactive liquid aluminum hydroxide gel. The aging characteristics are shown to be excellent.

SINCE ITS INTRODUCTION into therapeutics in 1934 by Einsel, Adams, and Myers (1), gelatinous liquid aluminum hydroxide gel, alone or in effective combination with other antacids such as magnesium hydroxide or magnesium trisilicate, has become the antacid of choice for the medical management of peptic ulcer and gastric hyperacidity. The literature is replete with reports of its successful use in the clinical treatment of these disorders (2–18). *In vitro* antacid evaluation tests carried out by many investigators (19–26) have shown that liquid aluminum hydroxide gel of proved clinical effectiveness yields both prompt and prolonged activity in the optimum pH range of 3 to 5. It also maintains this activity during a long shelf life.

In contrast with the ideal behavior of the liquid product, dried aluminum hydroxide has been shown (24, 27) to be slow in reacting with gastric strength acid, markedly inhibited in that action by pepsin, and to exhibit a diminution in reaction rate on aging.

This paper and others to follow will present *in vitro* antacid evaluation data on several new aluminum hydroxide gels in dry form which compare favorably in their antacid action with liquid aluminum hydroxide gel. The new dried gels have been designed to exhibit (*a*) promptness of reaction with gastric strength acid, (*b*) prolonged reactivity in the pH range of 3 to 5 in the presence of pepsin, (*c*) minimum loss of reactivity on aging, and (*d*) to be made generally available at moderate cost. The variety of dried gels to be made available will enable the pharmaceutical manufacturer to select a product which best meets his requirement.

This paper will describe two new aluminum hydroxide–magnesium carbonate dried gels (AHMC) which are designated as type F-MA11 and type F-MA12. They differ only in the mole ratio of alumina to magnesia present which is 2:1 and 1.25:1, respectively. When a highly reactive and stable aluminum hydroxide gel is intimately blended with a freshly prepared, low temperature, magnesium carbonate gel and the whole carefully reduced to dry form as by spray drying, the resulting white, free flowing, dense, tasteless powder is found to rehydrate readily and react rapidly with gastric strength acid containing pepsin.

EXPERIMENTAL

The average composition and physical properties of the two new AHMC dried gels are shown in Table I.

TABLE I.—ANALYSES OF TYPICAL SAMPLES OF AHMC DRIED GEL

	F-MA11	F-MA12
Aluminum oxide (Al_2O_3)	42.0%	37.1%
Magnesium oxide (MgO)	8.3%	11.7%
Carbonated (CO_2)	20.0%	16.2%
pH 4% aqueous suspension	9.2	9.1
Acid consuming capacity, (ml. 0.1 *N* HCl per Gm.)	287	286
Al_2O_3:MgO Mole Ratio	2:1	1.25:1
Apparent density (cc./Gm.)	0.44	0.2 or 0.4[a]

[a] Depending on method of drying.

X-ray Diffraction Studies.—X-ray diffraction studies were made using the Debye-Scherrer powder technique with thin-wall glass capillaries 0.30 mm. O. D. and 0.25 mm. I. D. The exposures were made for two hours at 35 mv. and 20 ma. on the X-ray tube. Exposures were made of aluminum hydroxide dried gel, magnesium carbonate gel dried, the new AHMC dried gels, and a dry blend of aluminum hydroxide dried gel with magnesium carbonate powder. Aluminum hydroxide dried gel and AHMC dried gels gave no pattern, indicating that

* Received September 2, 1959, from the Research Laboratory, Reheis Co., Inc., Berkeley Heights, N. J.
Presented to the Scientific Section, A. PH. A. Cincinnati meeting, August 1959.

they are essentially, if not wholly, amorphous. The dry blend gave a faint pattern with lines corresponding to magnesium carbonate. The dry magnesium carbonate gave a very distinct pattern.

Infrared Spectra.—Rock salt infrared spectra (2 to 15 μ) were made on samples of AHMC dried gel as well as each component dried separately. Nujol as well as hexachlorobutadiene (HCBD) mulls were made. A careful examination of the absorption bands of the two components showed that they were present in the absorption spectra of AHMC with no new bands present in the latter. It was concluded that AHMC dried gels are simple mixtures and not new compounds. The infrared spectrum of magnesium carbonate showed that the material chemically is intermediate between $MgCO_3$ and $3\ MgCO_3 \cdot Mg(OH)_2 \cdot 3H_2O$.

Antacid Activity.—Four principal *in vitro* methods are used to evaluate antacids in our laboratories as follows: (*a*) acid consuming capacity, (*b*) Reheis reaction velocity test, (*c*) Mutch reaction velocity test, and (*d*) procedure of Holbert, Noble, and Grote modified.

Acid Consuming Capacity.—This measures the volume of 0.1*N* HCl with which 1 Gm. of sample may react at 37.5° for one hour with an excess of acid present. The excess acid is back titrated to the Toepfers reagent end point (pH 3.5). Since this test does not show rate of change and since it employs an excess of acid throughout, it has been classified as generally unsatisfactory (21, 28–30). Values obtained for various antacid chemicals are shown in Table II.

TABLE II.—ACID CONSUMING CAPACITY OF VARIOUS ANTACIDS

Sample	ml. 0.1 *N* HCl/Gm. Sample
AHMC type F-MA11	287
AHMC type F-MA12	286
Aluminum dihydroxy aminoacetate	175
Aluminum dihydroxy sodium carbonate	267
Sodium polyhydroxy aluminum monocarbonate hexitol complex	275
Aluminum hydroxide dried gel	267
Sodium bicarbonate	120
Magnesium carbonate	220
Calcium carbonate	210
Magnesium trisilicate	115
Magnesium oxide	495

Reheis Reaction Velocity Test.—This test has been used by the author in our laboratories for eighteen years as a relatively quick method of assessing reaction rates of alumina gels. The weight of sample containing the equivalent of 0.5 Gm. Al_2O_3 is added to 100 ml. 0.1*N* HCl at 37.5° and the whole shaken until the pH rises to about 3.5 (Toepfers reagent). The time is noted and is that required for the sample to react with 34% of the theoretical amount of acid.

A highly reactive alumina gel gives values of ten to twenty seconds. A newly prepared sample of spray dried gel may react in one hundred and twenty seconds and two hundred and forty seconds after three months storage at room temperature. After four years of storage the time may increase to six hundred and sixty seconds. By contrast, samples of AHMC yield values of twenty seconds when new and similar values after two years aging at room temperature. Typical values for various aluminum-containing antacids are shown in Table III.

TABLE III.—REHEIS REACTION VELOCITY VALUES FOR VARIOUS ALUMINUM ANTACIDS

Sample	Seconds
Aluminum hydroxide gel U. S. P.	15
Aluminum hydroxide dried gel U. S. P.	240
AHMC type F-MA11	22
AHMC type F-MA12	20
Sodium polyhydroxy aluminum monocarbonate hexitol complex	35
Aluminum dihydroxy aminoacetate	29
Aluminum dihydroxy sodium carbonate	15
Aluminum hydroxide dried gel U. S. P.-magnesium carbonate U. S. P. dry blend (4:1)	247

Mutch Reaction Velocity Test.—This test which was described by Mutch (31) in 1946 is similar to the Reheis reaction velocity test described above except that it uses 78% of the theoretical amount of acid per weight of alumina. The time is that required for the sample containing the equivalent of 0.10 Gm. $Al(OH)_3$ to react with 30 ml. 0.1*N* HCl at 37.5° to the Toepfers reagent end point. Typical values for various aluminum-containing chemicals are shown in Table IV.

TABLE IV.—MUTCH REACTION VELOCITY VALUES FOR VARIOUS ALUMINUM ANTACIDS

Sample	Seconds
Aluminum hydroxide gel U. S. P.	40
Aluminum hydroxide dried gel U. S. P.	1,080
AHMC type F-MA11	54
AHMC type F-MA12	50
Sodium polyhydroxy aluminum monocarbonate hexitol complex	275
Aluminum dihydroxy aminoacetate	103
Aluminum dihydroxy sodium carbonate	70
Aluminum hydroxide dried gel U. S. P.-magnesium carbonate U. S. P. dry blend (4:1)	1,570

Procedure of Holbert, Noble, and Grote Modified.—In 1948 Holbert, Noble, and Grote (28) published an *in vitro* method which was adapted from the carefully worked-out procedure of Johnson and Duncan (21). This made use of the concept of representing the secretion of fresh gastric juice and also continuous loss of gastric juice–antacid mixture through the pylorus. Holbert, *et al.*, added a 2-Gm. dose of antacid to 150 ml. of artificial gastric juice at 37.5° with constant agitation, and after ten minutes withdrew 20 ml. of mixture and replaced it with 20 ml. of fresh artificial gastric juice. This withdrawal and replacement was carried out periodically every ten minutes until the pH fell below 3.5. Murphey (27) also used this method with an artificial gastric juice consisting of 2.0 Gm. pepsin N. F. per liter of pH 1.5 hydrochloric acid.

We have adapted this method with the following changes which we feel impart a higher degree of precision and insures a greater reproducibility of results.

A dose of antacid is added to the equivalent of 150 ml. artificial gastric juice at 37.5 ± 1° contained in a

jacketed, baffled, glass vessel provided with a glass and reference electrode, thermocompensator, agitator, and overflow device. The artificial gastric juice is pH 1.5 hydrochloric acid (0.0316 *N*) containing 2.0 Gm. pepsin N. F. per liter. After ten minutes, additional gastric juice at 37.5 ± 1° is added continuously at the equivalent of 120 ml. per hour by means of a Milton Roy controlled volume "mini pump." A jacketed, 3-gallon glass reservoir of artificial gastric juice is maintained at 37.5° by means of an Aminco constant temperature water circulating bath. Excess gastric juice–antacid mixture is allowed to flow continuously from the glass reactor at the equivalent of 120 ml. per hour.

The apparatus designed for this purpose is shown in Figs. 1 and 2. The pH is measured by means of a Beckman model W pH meter which is connected to a Weston strip chart recorder operating with a chart speed of six inches per hour. The pH meter indicates and records values between 2.0 and 12.0. In practice, the actual amounts and sizes are four times those stated above to avoid crowding into a small container. Thus, 600 ml. of artificial gastric juice are added to a jacketed, 1-liter, glass vessel provided with an overflow tube at the 650 ml. level. The agitator is a two-inch, three-bladed, marine type propeller which operates at exactly 400 r. p. m. Glass baffles prevent swirling in the reaction vessel. The pumping rate for artificial gastric juice is 480 ml.

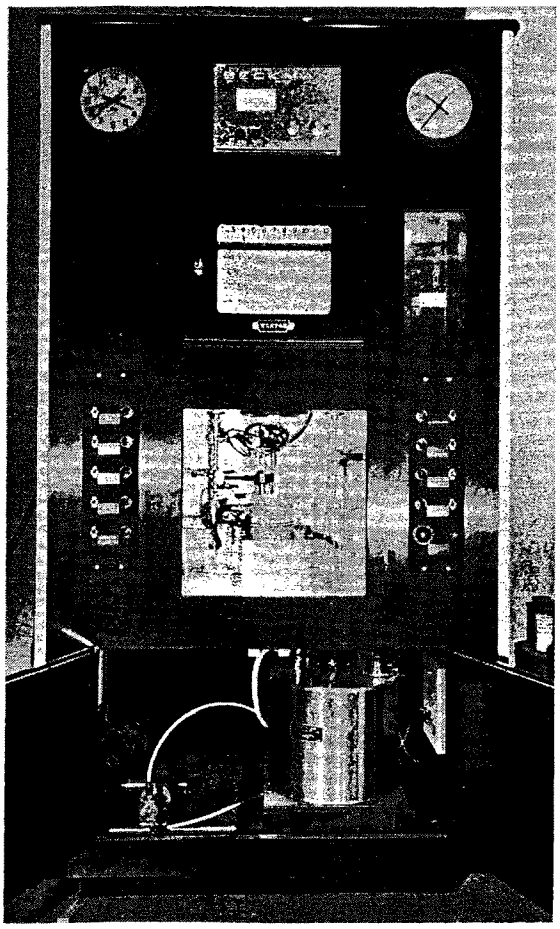


Fig. 1.—Automated apparatus for *in vitro* evaluation of antacid activity.

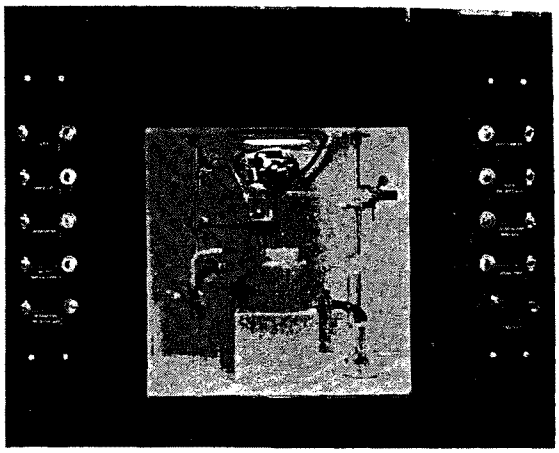


Fig. 2.—Close-up of cubicle showing details of glass reaction cell.

± 24 ml. per hour. The overflow is also at 480 ml. per hour. The sample size is four times the dose size. After addition of the sample to the glass reaction cell, the interval timer is started and pH values manually recorded every minute up to ten minutes, after which the constant addition of gastric juice is started. With the automation provided, the apparatus needs no further attention until the run is completed, which is usually when the pH has gone below 3.0. The average run is one hundred and twenty minutes. The reproducibility of results is very high.

When evaluating dry powders, 2, 4, or 8 Gm. (corresponding to doses of 0.5, 1, and 2 Gm., respectively) are dispersed in 35 ml. of water and poured in at time zero. Sucking tablets are ground to 100% through 100 mesh before dispersing in 35 ml. of water. Disintegrating types of tablets are dropped into 35 ml. of water and allowed to hydrate and disintegrate before adding. Liquid antacids are added directly to the glass reaction cell.

More than 800 two-hour evaluations have been made since late 1955 including countless samples which have been submitted by various pharmaceutical manufacturers. Many samples were blind samples to insure complere objectivity. Results have been treated on a highly confidential basis. Some results obtained on various antacid chemicals are shown in Table V and plotted in Figs. 3–15. Results obtained on the most widely used liquid commercial antacids are shown in Table VI, and on tablet preparations in Table VII.

Effect of Pepsin.—To demonstrate the effect of pepsin in artificial gastric juice on the antacid activity of dried aluminum hydroxide gel U. S. P. as measured by the modified procedure of Holbert, Noble, and Grote, runs were made on 1.0- and 2.0-Gm. samples with and without pepsin. The data are shown in Table VIII and Fig. 16.

Liquid aluminum hydroxide gel is not inhibited in this manner by pepsin. The full significance of this fact is not yet understood. AHMC dried gels do not show such inhibition by gastric pepsin.

Effect of Age.—The antacid activity of four-year old samples of AHMC dried gel, aluminum dihydroxy aminoacetate, and aluminum dihydroxy sodium carbonate was determined by the Holbert, Noble, and Grote method on the basis of 1-Gm. doses.

TABLE V.—*In Vitro* EVALUATION OF ANTACID ACTIVITY OF VARIOUS ANTACID CHEMICALS[a,b]

Time (min.)	1				2		3			4			5		
	5 ml.	10 ml.	12.5 ml.	15 ml.	1 Gm.	2 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	2.6	3.8	3.9	3.9	2.0	2.2	2.7	4.0	4.1	2.4	3.5	4.4	2.1	3.0	3.8
2	3.8	3.9	3.9	4.0	2.0	2.3	3.6	4.1	4.3	2.8	3.9	4.5	2.7	3.7	4.0
3	3.9	3.9	4.0	4.0	2.1	2.4	3.8	4.2	4.3	3.2	4.0	4.7	3.2	3.9	4.1
4	3.9	3.9	4.0	4.1	2.1	2.4	3.9	4.2	4.4	3.7	4.1	4.8	3.4	3.9	4.1
5	3.9	3.9	4.0	4.1	2.1	2.5	4.0	4.2	4.4	4.0	4.1	4.9	3.6	4.0	4.1
10	3.9	3.9	4.0	4.2	2.3	3.3	4.1	4.3	4.5	4.2	4.2	5.3	4.0	4.2	4.2
20	3.9	3.9	4.0	4.2	2.9	4.0	4.1	4.3	4.4	4.2	4.2	5.1	4.0	4.2	4.2
30	3.9	3.9	4.0	4.2	3.9	4.0	4.1	4.3	4.4	4.2	4.2	4.8	4.0	4.1	4.2
40	3.9	3.9	4.0	4.2	3.9	4.0	4.1	4.2	4.3	4.2	4.2	4.7	3.8	4.1	4.2
50	3.9	3.9	4.0	4.2	3.8	4.0	4.0	4.2	4.3	4.2	4.1	4.5	3.6	4.0	4.2
60	3.8	3.9	4.0	4.1	3.8	4.0	4.0	4.2	4.3	4.1	4.1	4.5	3.3	4.0	4.2
70	3.5	3.9	4.0	4.1	3.7	4.0	3.9	4.2	4.3	3.9	4.1	4.4	3.0	3.9	4.2
80	3.0	3.9	4.0	4.1	3.5	3.9	3.7	4.2	4.3	3.6	4.0	4.3	2.8	3.8	4 2
90	2.6	3.8	3.9	4.1	3.2	3.9	3.5	4.1	4.2	3.2	4.0	4.3	2.7	3.6	4.1
100	2.4	3.8	3.9	4.1	3.0	3.9	3.1	4.1	4.2	2.9	4.0	4.3	2.5	3.4	4.1
110	2.2	3.7	3.9	4.1	2.8	3.8	2.8	4.1	4.2	2.7	3.9	4.2	2.4	3.2	4.1
120	2.1	3.4	3.8	4.1	2.6	3.7	2.6	4.0	4.2	2.5	3.9	4.2	2.3	3.0	4.0

Time min.	6			7			8		9			10		
	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.1 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	3.1	3.8	4.2	2.0	2.0	2.3	2.3	3.6	2.0	2.0	2.0	6.6	7.2	7.6
2	3.5	4.0	4.3	2.0	2.0	2.5	2.9	3.8	2.0	2.2	2.3	6.9	7.6	7.8
3	3.6	4.1	4.4	2.0	2.0	2.7	3.5	3.9	2.0	2.6	2.9	7.1	7.8	7.9
4	3.7	4.1	4.5	2.0	2.1	2.9	3.7	4.0	2.0	4.1	4.2	7.2	7.9	8.0
5	3.8	4.2	4.5	2.1	2.2	3.0	3.7	4.0	2.6	5.3	5.7	7.8	8.0	8.0
10	3.9	4.3	4.9	2.4	2.5	3.2	3.9	4.0	2.2	6.8	7.2	7.2	7.7	7.8
20	3.6	4.2	4.6	2.5	2.8	3.2	3.8	4.0	2.4	6.7	7.2	7.6	7.6	7.8
30	3.2	4.1	4.3	2.3	2.8	3.1	3.7	4.0	2.4	6.6	7.1	7.0	7.6	7.8
40	3.1	4.0	4.3	2.3	2.7	3.0	3.7	4.0	2.3	6.3	7.1	6.8	7.6	7.7
50	3.0	3.9	4.2	2.3	2.7	3.0	3.6	3.9	2.2	5.8	7.0	6.5	7.5	7.7
60	2.9	3.9	4.2	2.2	2.6	2.9	3.5	3.9	2.1	4.8	7.0	6.2	7.4	7.7
70	2.8	3.8	4.2	2.1	2.6	2.9	3.2	3.9	2.1	3.9	6.9	5.3	7.3	7.7
80	2.6	3.8	4.1	2.1	2.5	2.8	2.8	3.8	2.1	3.2	6.7	3.0	7.1	7.6
90	2.4	3.7	4.1	2.1	2.4	2.7	2.5	3.8	2.0	2.7	6.5	2.6	6.9	7.5
100	2.3	3.6	4.0	2.0	2.3	2.7	2.3	3.7	2.0	2.4	6.3	2.4	6.7	7.5
110	2.2	3.6	4.0	2.0	2.3	2.6	2.2	3.5	2.0	2.3	5.6	2.3	6.4	7.4
120	2.1	3.5	4.0	2.0	2.2	2.5	2.1	3.4	2.0	2.2	5.6	2.2	5.8	7.3

Time, min.	11			12			13		
	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.	0.5 Gm.	1.0 Gm.	2.0 Gm.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	6.2	8.9	9.1	5.7	5.8	5.9	5.4	6.4	6.9
2	7.2	9.0	9.1	5.8	5.8	6.0	5.5	6.4	7.0
3	8.6	9.0	9.2	5.8	5.8	6.0	5.5	6.5	7.0
4	8.7	9.1	9.2	5.9	5.9	6.0	5.5	6.5	7.0
5	8.8	9.1	9.2	5.9	5.9	6.0	5.5	6.5	7.1
10	8.9	9.1	9.2	6.0	6.0	6.1	5.6	6.7	7.2
20	8.9	8.9	9.1	5.9	6.0	6.1	4.5	6.7	7.3
30	7.8	8.8	9.1	5.9	6.0	6.1	2.8	6.7	7.2
40	7.6	8.8	9.1	5.9	6.0	6.1	2.5	6.6	7.2
50	7.3	8.7	9.1	5.8	6.0	6.1	2.3	6.5	7.2
60	6.9	8.6	9.0	5.7	6.0	6.1	2.2	6.2	7.2
70	6.4	8.5	9.0	4.7	6.0	6.1	2.1	5.3	7.2
80	5.6	8.3	8.9	3.2	5.9	6.1	2.1	2.9	7.1
90	4.9	8.2	8.9	2.8	5.9	6.1	2.0	2.6	7.0
100	4.4	8.0	8.9	2.5	5.8	6.1	2.0	2.6	6.8
110	3.9	7.7	8.8	2.3	5.8	6.1	2.0	2.2	6.5
120	3.2	7.4	8.7	2.2	5.7	6.0	2.0	2.2	6.3

[a] Time *versus* pH at various dose levels, procedure of Holbert, Noble, and Grote modified.
[b] Identification of samples:

1. Aluminum hydroxide gel U. S. P.
2. Aluminum hydroxide dried gel U. S. P.
3. AHMC type F-MA11.
4. AHMC type F-MA12.
5. Aluminum dihydroxy aminoacetate.
6. Aluminum dihydroxy sodium carbonate.
7. Aluminum proteinate.
8. Sodium polyhydroxy aluminum monocarbonate hexitol complex.
9. Magnesium trisilicate U. S. P.
10. Magnesium carbonate U. S. P.
11. Magnesium hydroxide N. F.
12. Calcium carbonate U. S. P.
13. Sodium bicarbonate U. S. P.

2.0 Gm.
1.5
3.8
4.0
4.1
4.1
4.1
4.2
4.2
4.2
4.2
4.2
4.2
4.2
4 2
4.1
4.1
4.1
4.0

0 2.0 n. Gm.
5 1.5
2 7.6
6 7.8
8 7.9
9 8.0
0 8.0
7 7.8
6 7.8
6 7.8
6 7.7
5 7.7
4 7.7
3 7.7
1 7.6
9 7.5
7 7.5
4 7.4
8 7.3

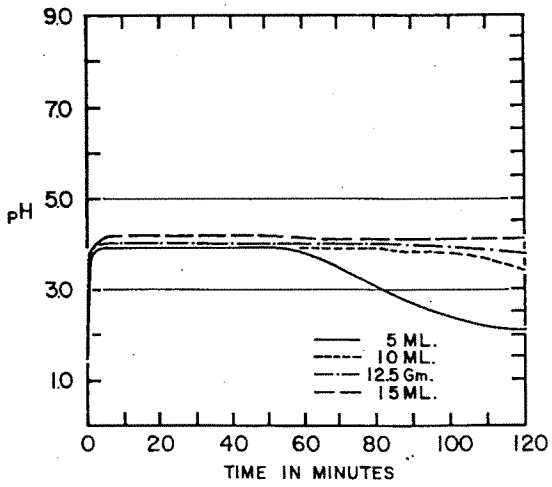


Fig. 3.—Aluminum hydroxide gel U. S. P. Procedure of Holbert, Noble, and Grote modified.

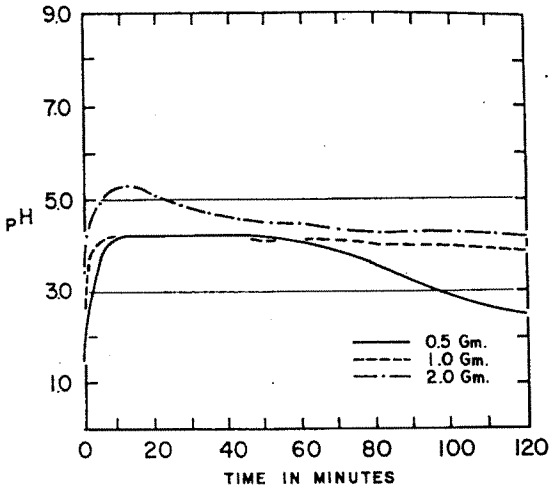


Fig. 6.—AHMC type F-MA12, procedure of Holbert, Noble, and Grote modified.

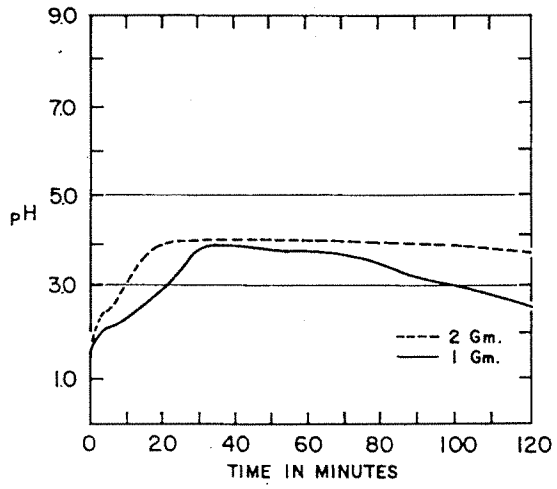


Fig. 4.—Aluminum hydroxide dried gel U. S. P., procedure of Holbert, Noble, and Grote modified.

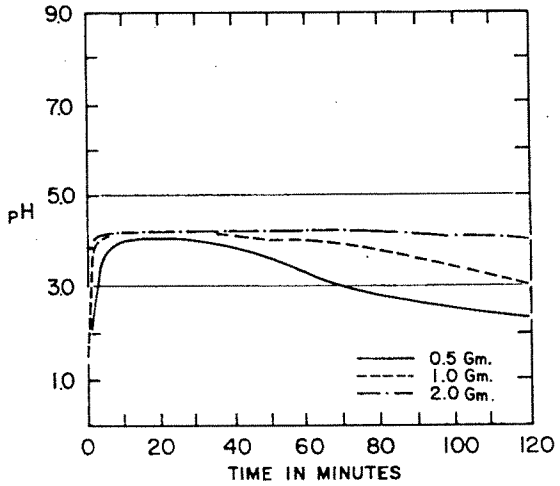


Fig. 7.—Aluminum dihydroxy aminoacetate, procedure of Holbert, Noble, and Grote modified.

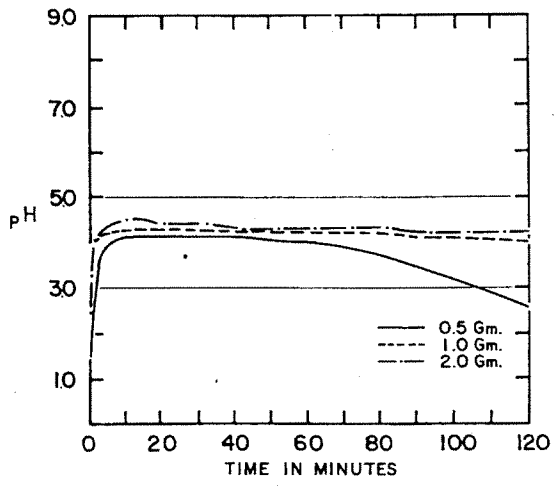


Fig. 5.—AHMC type F-MA11, procedure of Holbert, Noble, and Grote modified.

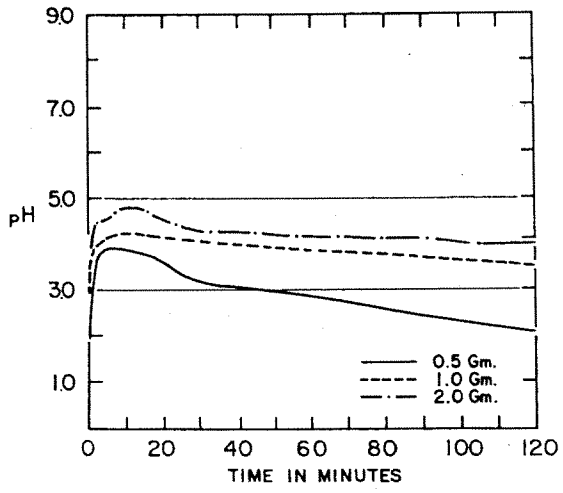


Fig. 8.—Aluminum dihydroxy sodium carbonate, procedure of Holbert, Noble, and Grote modified.

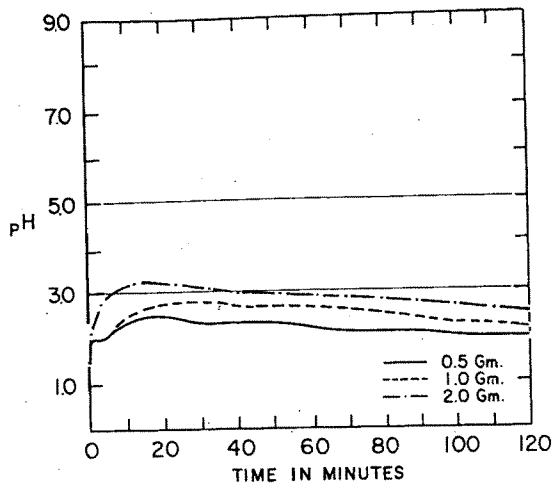


Fig. 9.—Aluminum proteinate, procedure of Holbert, Noble, and Grote modified.

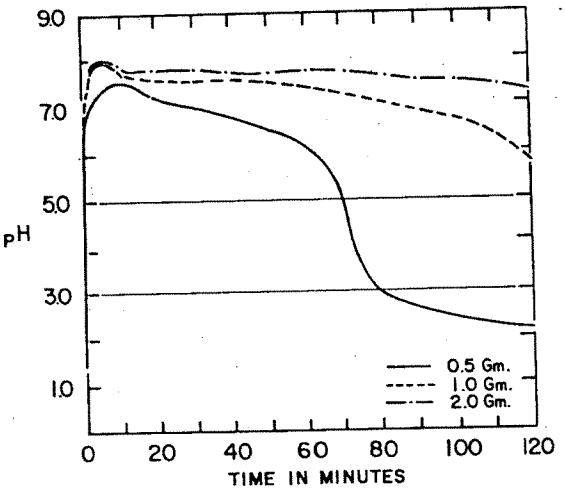


Fig. 12.—Magnesium carbonate U. S. P., procedure of Holbert, Noble, and Grote modified.

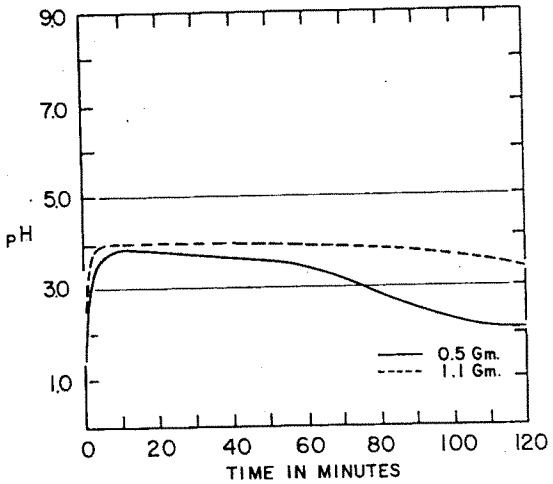


Fig. 10.—Sodium polyhydroxy aluminum monocarbonate hexitol complex, procedure of Holbert, Noble, and Grote modified.

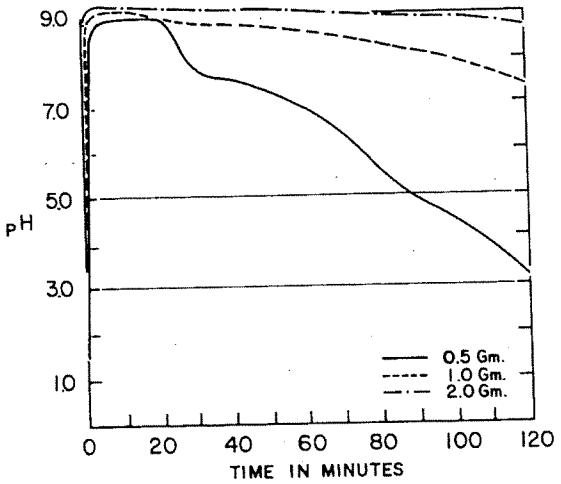


Fig. 13.—Magnesium hydroxide N. F., procedure of Holbert, Noble, and Grote modified.

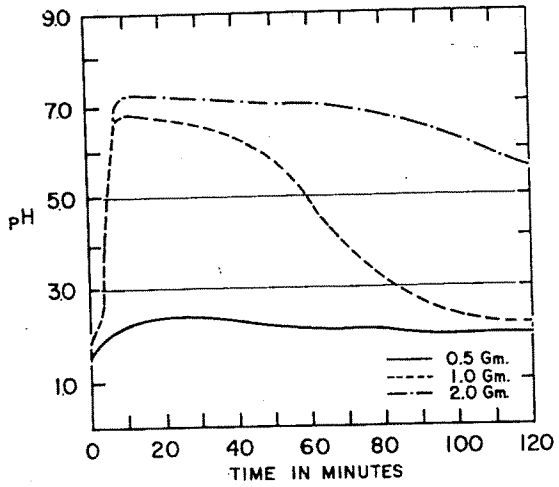


Fig. 11.—Magnesium trisilicate U. S. P., procedure of Holbert, Noble, and Grote modified.

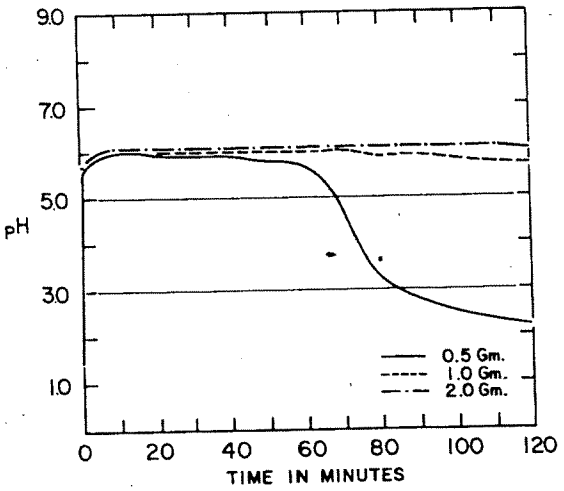


Fig. 14.—Calcium carbonate, procedure of Holbert, Noble, and Grote modified.

TABLE VI.—*In Vitro* EVALUATION OF VARIOUS COMMERCIAL LIQUID ANTACIDS[a, b]

Time, min.	14 15 ml.	15 15 ml.	16 15 ml.	17 4 ml.	17 8 ml.	17 15 ml.	18 15 ml.	19 15 ml.	20 15 ml.	21 5 ml.	21 10 ml.	22 4 ml.	23 25 ml.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	2.6	4.0	3.9	2.1	3.0	3.8	5.6	4.2	3.9	2.7	3.7	2.0	3.0
2	3.1	4.1	4.0	2.5	3.3	4.0	5.7	4.2	4.0	3.3	3.9	2.0	3.0
3	3.5	4.1	4.1	2.7	3.4	4.1	5.7	4.3	4.0	3.8	4.0	2.0	3.1
4	3.7	4.1	4.1	2.9	3.5	4.2	5.8	4.3	4.0	3.9	4.1	2.0	3.1
5	3.8	4.1	4.1	3.0	3.6	4.3	5.8	4.3	4.1	4.0	4.1	2.0	3.1
10	4.1	4.1	4.2	3.2	3.8	4.6	5.9	4.4	4.1	4.1	4.2	2.0	3.2
20	4.1	4.1	4.2	3.0	3.6	4.3	5.8	4.2	4.1	4.2	4.2	2.0	3.0
30	4.2	4.0	4.2	2.8	3.5	4.1	5.7	4.2	4.0	4.3	4.2	2.0	2.9
40	4.2	4.0	4.3	2.7	3.4	3.9	5.5	4.1	4.0	4.3	4.3	2.0	2.9
50	4.2	4.0	4.3	2.5	3.2	3.7	5.4	4.1	3.9	4.3	4.3	2.0	2.8
60	4.1	4.0	4.3	2.3	3.1	3.6	5.2	4.1	3.9	4.2	4.3	2.0	2.8
70	4.1	3.9	4.3	2.2	2.9	3.5	5.0	4.0	3.8	4.1	4.3	2.0	2.8
80	4.0	3.9	4.3	2.1	2.7	3.4	4.7	4.0	3.6	4.0	4.2	2.0	2.7
90	3.9	3.9	4.2	2.1	2.5	3.4	4.5	4.0	3.5	4.0	4.2	2.0	2.7
100	3.7	3.8	4.0	2.0	2.4	3.3	4.4	3.9	3.5	3.8	4.1	2.0	2.7
110	3.5	3.8	3.9	2.0	2.3	3.3	4.3	3.8	3.3	3.6	4.0	2.0	2.6
120	3.0	3.7	3.8	2.0	2.2	3.2	4.2	3.7	..	3.3	3.9	2.0	2.6

[a] Time *versus* pH at various dose levels, procedure of Holbert, Noble, and Grote modified.
[b] Identification of samples:

14. Aluminum hydroxide gel U. S. P., brand A.
15. Aluminum hydroxide gel U. S. P., brand B.
16. Aluminum–magnesium hydroxide.
17. Aluminum hydroxide (low reactive)–magnesium trisilicate.
18. Aluminum hydroxide with magnesium trisilicate.
19. Magnesium trisilicate (650 mg.) in aluminum hydroxide (322 mg.) per 5 ml.
20. Aluminum hydroxide gel with magnesium hydroxide.
21. Aluminum hydroxide gel–magnesium hydroxide–sorbitol.
22. Bismuth aluminate cream.
23. Aluminum phosphate gel U. S. P.

TABLE VII.—*In Vitro* EVALUATION OF VARIOUS COMMERCIAL ANTACID TABLETS[a, b]

Time, min.	24 1 Tab.	24 2 Tab.	25 1 Tab.	25 2 Tab.	26 1 Tab.	26 2 Tab.	27 1 Tab.	27 2 Tab.	27 4 Tab.	28 1 Tab.	28 2 Tab.	28 4 Tab.	29 1 Tab.	29 2 Tab.	29 4 Tab.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	2.0	2.0	2.0	2.0	2.2	3.8	2.8	3.5	3.5	2.0	2.7	4.1	2.0	3.9	3.3
2	2.0	2.1	2.0	2.2	3.3	4.0	3.4	3.9	3.8	2.0	3.3	5.0	2.1	4.6	4.4
3	2.0	2.1	2.0	2.4	3.7	4.1	3.6	4.1	3.9	2.4	3.7	5.5	2.3	5.0	4.9
4	2.0	2.2	2.1	2.6	3.8	4.1	3.9	4.1	3.9	2.6	3.8	5.7	2.4	5.4	5.3
5	2.0	2.3	2.1	2.8	3.8	4.1	3.9	4.2	4.0	2.7	4.0	5.9	2.6	5.7	5.7
10	2.4	3.0	2.3	3.4	3.9	4.2	4.0	4.2	4.1	2.9	5.2	6.1	3.2	6.4	6.6
20	3.5	3.7	2.3	3.3	4.0	4.2	3.9	4.2	4.2	2.8	4.6	5.9	2.9	5.0	5.1
30	3.5	3.7	2.3	3.1	4.0	4.2	3.8	4.2	4.2	2.6	4.2	5.7	2.7	4.8	5.0
40	3.5	3.7	2.2	2.9	4.0	4.2	3.6	4.2	4.2	2.4	3.8	5.6	2.6	4.7	4.9
50	3.5	3.7	2.2	2.7	4.0	4.1	3.4	4.2	4.1	2.3	3.4	5.4	2.5	4.5	4.8
60	3.4	3.7	2.1	2.6	4.0	4.1	3.0	4.1	4.1	2.2	3.3	5.2	2.3	4.3	4.6
70	3.4	3.6	2.1	2.4	3.9	4.1	2.8	4.1	4.1	2.2	3.1	4.9	2.3	4.2	4.4
80	3.3	3.5	2.0	2.3	3.7	4.1	2.6	3.9	4.0	2.1	3.0	4.6	2.2	4.0	4.3
90	3.2	3.5	2.0	2.2	3.4	4.1	2.5	3.7	3.9	2.0	2.9	4.1	2.1	3.7	4.2
100	3.1	3.3	2.0	2.1	2.9	4.0	2.3	3.5	3.6	2.0	2.7	3.7	2.1	3.5	4.2
110	3.0	3.1	2.0	2.1	2.6	4.0	2.2	3.2	3.3	2.0	2.6	3.3	2.0	3.2	4.1
120	2.9	3.0	2.0	2.0	2.4	4.0	2.1	2.9	3.1	2.0	2.5	3.0	2.0	2.9	4.0

Time, min.	30 1 Tab.	30 2 Tab.	30 3 Tab.	31 1 Tab.	31 2 Tab.	32 2 Tab.	33 2 Tab.	33 4 Tab.	34 1 Tab.	34 2 Tab.	34 4 Tab.	35 1 Tab.	35 2 Tab.	36* 1 Tab.	36* 2 Tab.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	2.0	3.0	3.6	2.0	2.8	2.0	2.8	3.5	2.4	3.6	5.3	3.5	4.0	5.2	5.1
2	2.3	3.8	3.8	2.1	3.4	2.0	3.4	4.0	2.9	3.9	6.2	3.6	4.1	5.3	5.4
3	2.6	3.9	3.9	2.2	3.7	2.1	3.7	4.2	3.2	4.0	6.6	3.7	4.1	5.4	5.5
4	2.7	4.0	4.0	2.3	3.8	2.1	3.9	4.3	3.4	4.0	6.9	3.8	4.2	5.4	5.5
5	3.2	4.0	4.0	2.5	3.9	2.1	4.0	4.5	3.5	4.1	7.1	4.0	4.2	5.5	5.6
10	3.8	4.0	4.0	3.2	4.0	2.5	4.2	6.7	3.8	4.3	7.6	4.1	4.2	5.6	5.7
20	3.6	4.0	4.0	3.4	4.0	2.8	4.3	7.1	3.8	4.4	7.8	3.9	4.1	5.2	5.5
30	3.4	4.0	4.0	3.5	4.0	2.8	4.3	6.8	3.7	4.3	7.7	3.6	4.0	5.2	5.5
40	3.0	4.0	4.0	3.3	4.0	2.8	4.2	6.4	3.6	4.2	7.5	3.3	4.0	5.0	5.5
50	2.6	4.0	3.9	3.1	3.9	2.8	4.1	5.7	3.5	4.0	7.1	3.1	3.9	4.7	5.4
60	2.4	3.9	3.9	2.9	3.9	2.8	4.0	4.9	3.4	3.9	6.5	2.9	3.8	4.2	5.4
70	2.2	3.9	3.9	2.7	3.8	2.7	3.9	4.4	3.3	3.8	5.9	2.7	3.6	3.1	5.3
80	2.1	3.8	3.8	2.6	3.7	2.5	3.8	4.2	3.2	3.8	5.2	2.6	3.5	2.6	5.2
90	2.0	3.6	3.7	2.5	3.6	2.4	3.8	4.0	3.0	3.7	4.6	2.4	3.3	2.4	5.1
100	2.0	3.3	3.7	2.4	3.5	2.4	3.7	3.8	2.9	3.7	4.3	2.3	3.2	2.2	4.8
110	2.0	2.9	3.5	2.3	3.3	2.3	3.6	3.7	2.7	3.6	4.0	2.2	3.0	2.1	4.3
120	2.0	2.7	3.4	2.2	3.1	2.3	3.5	3.6	2.6	3.5	3.8	2.1	2.9	2.1	3.0

TABLE VII (*continued*)

Time, min.	37 2 Tab.	38 1 Tabl	38 2 Tab.	38 4 Tab.	39 1 Tab.	39 2 Tab.	40 1 Tab.	40 2 Tab.	41 2 Tab.	42 2 Tab.	43 1 Tab.	43 2 Tab.	43 4 Tab.
0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1	6.0	4.5	5.7	6.2	5.5	6.0	5.4	6.0	2.2	3.5	3.9	4.1	4.3
2	6.2	5.1	6.2	7.1	5.7	6.3	5.7	6.2	2.8	3.8	4.0	4.3	4.8
3	6.3	5.4	6.6	7.9	5.8	6.5	5.9	6.4	3.3	3.9	4.1	4.4	5.2
4	6.3	5.6	7.0	8.2	5.9	6.6	6.0	6.4	3.9	3.9	4.1	4.6	5.4
5	6.4	5.7	7.5	8.3	6.0	6.7	6.1	6.5	4.4	3.9	4.1	4.7	5.6
10	6.5	6.1	8.2	8.6	6.2	7.1	6.3	6.7	5.5	4.0	4.1	5.1	5.8
20	6.3	5.7	7.9	8.4	6.9	6.1	6.3	6.5	5.2	4.0	4.0	4.5	4.9
30	6.2	5.0	7.6	8.3	5.9	6.7	6.2	6.5	4.5	4.0	3.9	4.3	4.8
40	6.2	4.3	7.1	8.1	5.8	6.4	6.1	6.5	3.9	4.0	3.9	4.2	4.7
50	6.2	3.6	6.7	7.9	5.7	6.3	6.0	6.5	3.5	3.9	3.8	4.1	4.5
60	6.2	3.0	6.3	7.7	5.4	6.1	5.7	6.4	3.3	3.9	3.6	4.1	4.4
70	6.1	2.6	5.9	7.5	4.9	6.0	4.9	6.4	2.9	3.9	3.2	4.0	4.3
80	6.0	2.5	5.4	7.2	4.6	6.0	4.0	6.3	2.7	3.8	2.8	4.0	4.2
90	5.9	2.3	4.7	7.0	4.1	5.8	3.7	6.2	2.5	3.7	2.5	3.9	4.2
100	5.7	2.2	4.0	6.7	3.6	5.7	3.5	6.1	2.4	3.5	2.3	3.8	4.1
110	5.3	2.2	3.3	6.5	3.1	5.5	3.3	5.8	2.3	3.3	2.2	3.7	4.0
120	4.2	2.1	2.9	6.2	2.8	5.2	3.1	5.1	2.2	3.0	2.1	3.5	4.0

[a] Time *versus* pH at various dose levels, procedure of Holbert, Noble, and Grote modified.
[b] Identification of samples:

24. Aluminum hydroxide dried gel (660 mg.).
25. Aluminum hydroxide dried gel (660 mg.).
26. AHMC type F-MA11 (660 mg.).
27. Aluminum dihydroxy aminoacetate (500 mg.).
28. Magnesium trisilicate (500 mg.) and aluminum hydroxide (250 mg.).
29. Aluminum–magnesium hydroxide (400 mg.).
30. Sodium polyhydroxy aluminum monocarbonate hexitol complex (320 mg.) calculated as aluminum hydroxide dried gel U. S. P.
31. Aluminum hydroxide (648 mg.) and magnesium trisilicate (324 mg.).
32. Aluminum hydroxide and magnesium trisilicate.
33. Aluminum hydroxide–glycine (450 mg.), magnesium oxide (60 mg.), and bellafoline (0.5 mg.).
34. Aluminum hydroxide–glycine (450 mg.) and magnesium oxide (60 mg.).
35. Aluminum dihydroxy sodium carbonate (330 mg.).
36. Calcium carbonate (510 mg.), magnesium carbonate (30 mg.), and magnesium trisilicate (40 mg.).
37. Calcium carbonate, magnesium carbonate, and magnesium trisilicate.
38. Calcium carbonate, magnesium trisilicate, and magnesium hydroxide.
39. Calcium carbonate, magnesium carbonate, and magnesium trisilicate.
40. Heavy magnesium carbonate (182 mg.), light magnesium carbonate (24 mg.), calcium carbonate (441 mg.), and aluminum hydroxide (223 mg.).
41. Regenol (100 mg.), magnesium trisilicate (100 mg.), aluminum hydroxide dried gel (90 mg.), calcium carbonate (100 mg.), magnesium carbonate (100 mg.), and egraine (45 mg.).
42. AHMC type F-MA11 (330 mg.) and activated attapulgite (130 mg.).
43. Sodium polyhydroxy aluminum monocarbonate hexitol complex (320 mg.), calculated as aluminum hydroxide driedgel U. S. P., and magnesium hydroxide (75 mg.).

TABLE VIII.—EFFECT OF PEPSIN ON ANTACID ACTIVITY OF DRIED ALUMINUM HYDROXIDE GEL U. S. P., TIME *versus* pH

Time, min.	Concentration of Pepsin 2.0 Gm./L. 1 Gm.	2.0 Gm./L. 2 Gm.	0.0 Gm./L. 1 Gm.	0.0 Gm./L. 2 Gm.
0	1.5	1.5	1.5	1.5
1	2.0[a]	2.1	2.0[a]	2.2
3	2.0[a]	2.2	2.0[a]	2.4
5	2.0[a]	2.3	2.0	2.5
10	2.0	2.6	3.9	4.2
20	2.2	3.3	4.1	4.2
30	2.4	4.0	4.2	4.2
40	2.6	4.0	4.2	4.2
50	2.7	4.0	4.2	4.2
60	2.8	4.0	4.2	4.2
70	2.8	4.0	4.2	4.2
80	2.7	3.9	4.2	4.2
90	2.6	3.9	4.2	4.2
100	2.6	3.8	4.2	4.2
110	2.5	3.7	4.2	4.1
120	2.4	3.5	4.1	4.1

[a] Indicates less than.

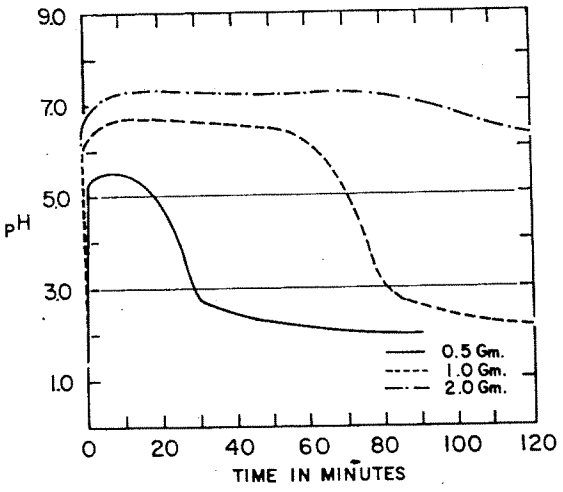


Fig. 15.—Sodium bicarbonate U. S. P., procedure of Holbert, Noble, and Grote modified.

The results, which are plotted in Fig. 17, show that AHMC is somewhat more reactive after four years storage at ambient temperatures than the other two samples.

Comparison with Dry Blend.—To demonstrate the difference in antacid properties between the new AHMC dried gels and a simple dry blend of aluminum hydroxide dried gel U. S. P. and magnesium carbonate U. S. P. having an Al_2O_3:MgO mole ratio of 2:1, the following experiment was performed. Four parts of dried aluminum hydroxide was thoroughly blended with one part of magnesium

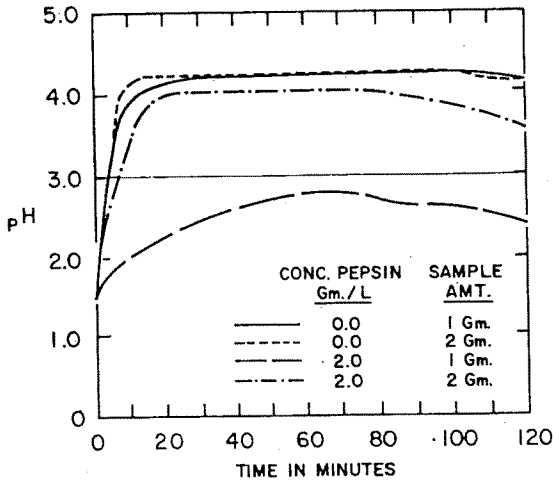


Fig. 16.—Effect of pepsin on antacid activity of dried aluminum hydroxide gel U. S. P., procedure of Holbert, Noble, and Grote modified.

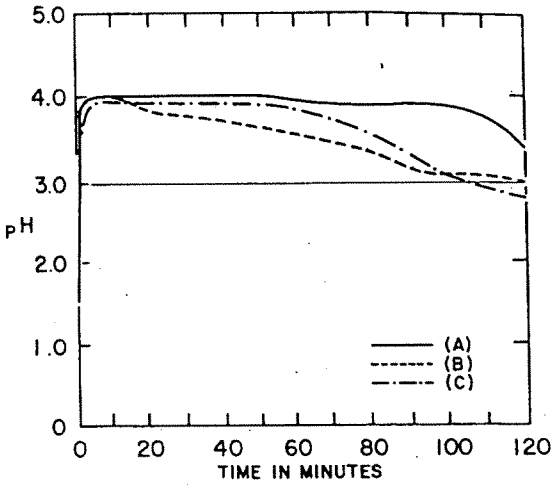


Fig. 17.—Antacid activity of four-year old samples of three aluminum antacids: (*A*) AHMC; (*B*) aluminum dihydroxy sodium carbonate; (*C*) aluminum dihydroxy aminoacetate; procedure of Holbert, Noble, and Grote modified.

carbonate, and the antacid activity of the blend was determined on the basis of 1 Gm. and 2 Gm. The data are shown in Table IX and plotted in Fig. 18.

TABLE IX.—ANTACID ACTIVITY COMPARISON OF AHMC WITH ALUMINUM HYDROXIDE–MAGNESIUM CARBONATE DRY BLEND (4:1)[a]

Time, min.	AHMC 1 Gm.	AHMC 2 Gm.	Aluminum Hydroxide–Magnesium Carbonate Dry Blend (Mole ratio—Al_2O_3:MgO—2:1) 1 Gm.	Dry Blend 2 Gm.
0	1.5	1.5	1.5	1.5
1	4.0	4.1	4.5	5.8
2	4.1	4.3	4.5	6.4
3	4.2	4.3	4.6	6.6
4	4.2	4.4	4.7	6.8
5	4.2	4.4	4.7	6.9
10	4.3	4.5	4.8	7.2
20	4.3	4.4	3.8	6.9
30	4.3	4.4	3.1	6.6
40	4.2	4.3	2.8	6.2
50	4.2	4.3	2.7	5.7
60	4.2	4.3	2.6	4.6
70	4.2	4.3	2.5	3.7
80	4.2	4.3	2.4	3.1
90	4.1	4.2	2.4	2.7
100	4.1	4.2	2.3	2.5
110	4.1	4.2	2.3	2.4
120	4.0	4.2	2.3	2.3

[a] Time *versus* pH, procedure of Holbert, Noble, and Grote.

RESULTS

The data in Tables III and IV show that by both reaction velocity tests AHMC dried gels are rapidly reactive with 0.1 *N* HCl at 37.5° and compare favorably with a highly reactive aluminum hydroxide gel U. S. P. (prepared from Reheis F-500 aluminum hydroxide compressed gel). Aluminum dihydroxy sodium carbonate, which is also shown to be rapidly reactive by the Reheis reaction velocity test, contains 306 mg. of sodium oxide for each 500 mg. of aluminum oxide. Aluminum dihydroxy aminoacetate and sodium polyhydroxy aluminum monocarbonate hexitol complex are only slightly less reactive than AHMC.

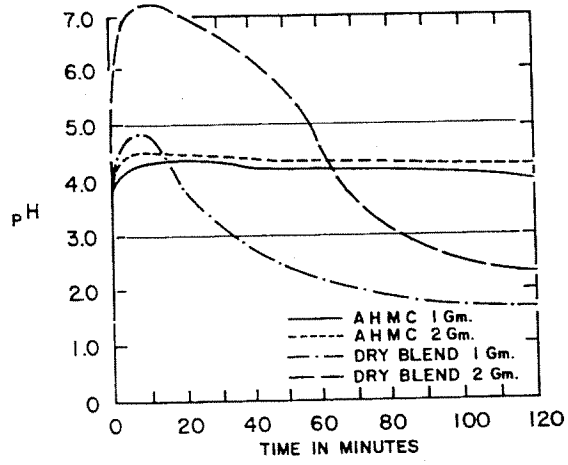


Fig. 18—Comparison of antacid activity of AHMC with aluminum hydroxide-magnesium carbonate dry blend (4:1), procedure of Holbert, Noble, and Grote modified.

The data in Table V, which are plotted in Figs. 3–15, show that both types of AHMC dried gel are very rapid and prolonged in their antacid activity in the pH range of 3 to 5 with artificial gastric juice. In this respect, they compare favorably with the ideal, a reactive liquid aluminum hydroxide gel.

The data plotted in Fig. 17 shows that AHMC retains this high degree of reactivity over a long period of time. Not a single substance tested shows better results than the AHMC dried gels. Table VII shows that the superior antacid characteristics of AHMC is retained in tablets as well. Hinkel, Fisher, and Tainter (25, 26) described a new highly reactive aluminum hydroxide (sodium polyhydroxy aluminum monocarbonate hexitol complex) which, when blended with magnesium hydroxide, forms the basis of an improved antacid tablet. The data for sample 43, Table VII indicates that the antacid characteristics of this new improved tablet are excellent and compare favorably with AHMC powder and tablets.

DISCUSSION

A new combination of two old antacids, aluminum hydroxide and magnesium carbonate, is shown to possess outstanding antacid properties. The principal method employed in this *in vitro* study is a very stringent test. It was Johnson and Duncan who first introduced the periodic replacement of antacid-acid mixture with the fresh gastric acid. They used an equivalent dose, which varied for each product tested, depending upon the acid neutralizing power of the substance. Holbert, Noble, and Grote (28) used a 2-Gm. sample and employed an artificial gastric juice instead of 0.1 *N* HCl Our modification consisted of (*a*) establishing an exact normality for the artificial gastric juice and (*b*) replacing it at a constant rate. The rate of change of pH with time during the first ten minutes is a function of its reactivity and, hence, the test is unexcelled for measuring promptness of buffering. Since, at the ten-minute interval an excess of antacid is usually present, the pH at ten minutes is a measure of the maximum pH that might be expected. The concentration of acid (pH 1.5–0.0316 *N*) in the artificial gastric juice also makes the test a very stringent one. A substance which reacts well with acid of this strength will react even more rapidly with a stronger acid. The constant replacement of reaction mixture with fresh gastric juice provides a system where the amount of ant-antacid is gradually diminishing while the supply of fresh acid is constant. A more stringent test for an antacid substance cannot be devised. One, of course, may vary the concentration and composition of the gastric juice and obtain a whole family of curves and data which is constant for the new gastric juice. We have used simulated gastric fluid U. S. P., which became official after our investigation was started. This is approximately 0.08 *N* but may vary depending on the concentration of hydrochloric acid used. Our results with this more concentrated gastric juice show that the total time in the pH range of 3 to 5 is less, but that the promptness of reaction and duration of action is similar for AHMC dried gel and liquid aluminum hydroxide gel.

The *in vitro* procedure, as employed, by us is not represented as being a duplication of the behavior of an antacid in the human stomach. It is perhaps the most severe method of comparing antacids that can be devised under conditions similar to those found in the stomach. It is doubtful whether any *in vivo* test so far described is fully adequate to differentiate between a large number of antacids. The final and true test must remain in the hands of competent clinicians.

Nature of Aluminum Hydroxide Gel.—Reactive aluminum hydroxide gel is a very dynamic system whose properties are dependent on the presence of immobilized watershells and the nature and amount of absorbed foreign anions and cations. The loss of protons, which are expelled from the hydration shells as a result of electrostatic attraction between an aluminum ion and an hydroxyl group in a neighboring hydration shell, brings about a polymerization. This structure can be stabilized by substances which help to retain the remaining protons in the hydration shells. Submicroscopic particles of magnesium carbonate is an excellent stabilizer of this structure.

SUMMARY

1. The preparation and properties of two new aluminum hydroxide–magnesium carbonate dried gels have been described.

2. *In vitro* evaluation of the antacid properties of AHMC dried gels by four methods demonstrate that its buffering action is very rapid and prolonged in the optimum pH range of 3 to 5. It compares favorably in this respect with reactive liquid aluminum hydroxide gels.

3. The outstanding antacid properties of AHMC are retained over a long period of time.

4. Of all other antacid chemicals tested in powder form, only aluminum dihydroxy aminoacetate, aluminum dihydroxy sodium carbonate, and sodium polyhydroxy aluminum monocarbonate hexitol complex exhibited prompt and prolonged activity in the pH range of 3 to 5.

5. *In vitro* antacid evaluation data on 30 of the most widely used antacids in liquid and tablet form are included for purposes of comparison.

REFERENCES

(1) Einsel, I. H., Adams, W. L., and Myers, V. C., *Am. J. Digest. Diseases*, **1**, 513(1934).
(2) Woldman, E. E., and Rowland, V. C., *Rev. Gastroenterol.*, **3**, 27(1936).
(3) Emery, E. S., Jr., and Rutherford, R. B., *Am. J. Digest. Diseases*, **5**, 486(1938).
(4) Eads, J. T., *ibid.*, **7**, 32(1940).
(5) Jones, C. R., Jr., *Am. J. Digest. Diseases Nutrition*, **4**, 99(1937).
(6) Connelly, A., and Hollander, F., *Rev. Gastroenterol.*, **9**, 354(1942).
(7) Kyger, E. R., Jr., Hashinger, E. H., and Wilbelmj, E. W., *Am. J. Digest. Diseases*, **6**, 363(1939).
(8) Kunstler, M. B., *Med. Record*, **149**, 268(1939).
(9) Bennett, T. I., and Gill, A. M., *Lancet*, **1**, 500(1939).
(10) Steigmann, F., *Illinois Med. J.*, **76**, 443(1939).
(11) Woldman, E. E., and Polan, C. G., *Am. J. Med. Sci.*, **198**, 155(1939).
(12) Fauley, G. B., Ivy, A. C., Terry, L., and Bradley, W. B., *Am. J. Digest. Diseases*, **5**, 792(1939).
(13) Cornell, A., Hollander, F., and Winkelstein, A., *ibid.*, **9**, 332(1942).
(14) McIntosh, J. F., and Sutherland, C. G., *Can. Med. Assoc. J.*, **42**, 140(1940).
(15) Hardt, L. L., and Brodt, L. P., *Arch. Surg.*, **55**, 584 (1947).
(16) Hardt, L. L., and Steigmann, F., *Am. J. Digest. Diseases*, **17**, 195(1950).
(17) Morrison, S., *Am. J. Gastroenterol.*, **21**, 301(1954).
(18) Collins, E. N., *J. Am. Med. Assoc.*, **127**, 899(1945).
(19) Rossett, N. E., and Flexner, J., *Ann. Internal Med.*, **21**, 119(1944).
(20) Rossett, N. E., and Flexner, J., *ibid.*, **18**, 193(1943).
(21) Johnson, E. H., and Duncan, J., *Quart. J. Pharm. and Pharmacol.*, **18**, 251(1945).
(22) Hammarlund, E. R., and Rising, L. W., THIS JOURNAL, **38**, 586(1949).
(23) Dale, J. K., and Booth, R. E., *ibid.*, **44**, 170(1955).
(24) Gwilt, J. R., Livingston, J. L., and Robertson, A., *J. Pharm. and Pharmacol.*, **10**, 770(1958).
(25) Hinkel, E. T., Jr., Fisher, M. P., and Tainter, M. L., THIS JOURNAL, **48**, 380(1959).
(26) Hinkel, E. T., Jr., Fisher, M. P., and Tainter, M. L., *ibid.*, **48**, 384(1959).
(27) Murphey, R. S., *ibid.*, **41**, 361(1952).
(28) Holbert, J. M., Noble, N., and Grote, I. W., *ibid.*, **37**, 292(1948).
(29) Holbert, J. M., Noble, N., and Grote, I. W., *ibid.*, **36**, 149(1947).
(30) Schenk, J., *Schweiz. med. Wochschr.*, **84**, 1418(1954).
(31) Mutch, N., *Quart. J. Pharm. and Pharmocol.*, **19** 490(1946).

28

365

968

AMA DRUG EVALUATIONS

SECOND EDITION

Prepared by the
AMA DEPARTMENT OF DRUGS

PUBLISHING SCIENCES GROUP, INC.
ACTON, MASSACHUSETTS

Printed in the United States of America.

International Standard Book Number: 0-88416-003-3

Library of Congress Catalog Number: 75-147249

CONTENTS

Preface III
Acknowledgments XI

GENERAL INFORMATION

Scope and Organization of Evaluations XVII
Dosage Recommendations XVIII
Timed-Release Preparations XIX
"Label as Such" and Related Matters XX
Use of Laboratory Studies to Monitor Adverse Reactions XX
Use of Drugs During Pregnancy XXII
Caution in Use of "Potent" Drugs XXII
Drug Interactions XXIII
Pharmacogenetics XXXVII
Official and Regulatory Agencies XLII

I CARDIOVASCULAR-RENAL AGENTS

1. Digitalis Glycosides 1
2. Antiarrhythmic Agents 9
3. Antianginal Agents 21
4. Peripheral Vasodilators 27
5. Agents Used in Hypotension and Shock 33
6. Antihypertensive Agents 45
7. Diuretics 65

II AGENTS AFFECTING BLOOD FORMATION, VOLUME, AND COAGULABILITY

8. Agents Used to Treat Deficiency Anemias 79
9. Anticoagulants 91
10. Blood, Blood Components, and Blood Substitutes 101
11. Hemostatics 109

III HOMEOSTATIC AND NUTRIENT AGENTS

12. Agents Used to Treat Hyperglycemia 123
13. Agents Used to Treat Hyperlipidemia 137
14. Vitamins and Sources of Vitamins 153
15. Miscellaneous Nutritional Agents 171
16. Replenishers and Regulators of Water, Electrolytes, and Nutrients 175
17. Blood Calcium Regulators 195

IV DRUGS USED IN ANESTHESIA

18. Local Anesthetics 205
19. General Anesthetics 223
20. Adjuncts to Anesthesia 235

V ANALGESICS, NARCOTIC ANTAGONISTS, AND AGENTS USED TO TREAT SPECIFIC PAINFUL DISORDERS

21. Strong Analgesics 249
22. Mild Analgesics 261
23. Narcotic Antagonists 277
24. Agents Used to Treat Migraine 281
25. Agents Used in Gout 287
26. Antirheumatic Agents 295

VI DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

27. Sedatives and Hypnotics 305
28. Antianxiety Agents 317
29. Antipsychotic Agents 325
30. Centrally Acting Skeletal Muscle Relaxants 339
31. Anticonvulsants 345
32. Antidepressants 359
33. Anorexiants 369
34. Analeptics 377

VII HORMONES AND AGENTS AFFECTING HORMONAL MECHANISMS

35. Adrenal Corticosteroids 381
36. Androgens and Anabolic Steroids 401
37. Estrogens, Progestagens, Oral Contraceptives, and Ovulatory Agents 411
38. Anterior Pituitary and Hypothalamic Hormones 433
39. Thyroid Hormones and Antithyroid Agents 441
40. Antidiuretics 453

VIII DRUGS USED IN RESPIRATORY AND ALLERGIC DISORDERS

41. Bronchodilators 457
42. Nasal Decongestants 467
43. Expectorants and Inhalants 475

44. Antitussive Agents 481
45. Antihistamines 491
46. Cold Remedies 499
47. Therapeutic Gases 505

IX ANTIMICROBIAL AGENTS

48. Penicillins 509
49. Cephalosporins 523
50. Erythromycin and Derivatives 529
51. Lincomycin and Clindamycin 533
52. Polymyxins 537
53. Tetracyclines 541
54. Chloramphenicol and Derivatives 551
55. Sulfonamides 555
56. Nitrofurans 565
57. Aminoglycoside Antibacterial Agents and Miscellaneous Antimicrobial Drugs 569
58. Antituberculous Agents 581
59. Antileprosy Agents 591
60. Antifungal Agents 595

X PARASITICIDAL AGENTS

61. Antimalarial Agents 607
62. Amebicides 617
63. Antitrypanosomal Agents 623
64. Antitrichomonal Agents 627
65. Anthelmintics 631
66. Scabicides and Pediculicides 641

XI AGENTS APPLIED LOCALLY

67. Antiseptics and Disinfectants 645
68. Dermatologic Agents 657

XII DRUGS USED IN OPHTHALMOLOGY

69. Agents Used to Treat Glaucoma 675
70. Mydriatics and Cycloplegics 687
71. Anti-infective and Anti-inflammatory Agents Used in Ophthalmology 701
72. Miscellaneous Ophthalmic Preparations 721

XIII OTOLOGIC AGENTS

73. Topical Otic Preparations 731

XIV DRUGS USED TO TREAT NEUROMUSCULAR DISORDERS

74. Antiparkinsonism Agents 739
75. Agents Used in Myasthenia Gravis 749

XV DIAGNOSTIC AGENTS

76. Radiopaque Media 753
77. Miscellaneous Diagnostic Aids 761

XVI GASTROINTESTINAL AGENTS

78. Antispasmodics 773
79. Antacids 785
80. Antidiarrheals 791
81. Laxatives and Agents Affecting Fecal Consistency 799
82. Anorectal Preparations 807
83. Miscellaneous Gastrointestinal Agents 811
84. Emetics 817
85. Antiemetics 819

XVII SMOOTH MUSCLE STIMULANTS

86. Stimulants of Gastrointestinal and Urinary Tracts 829
87. Oxytocics 831

XVIII ONCOLYTIC AGENTS

88. Antineoplastic Agents 835

XIX IMMUNOLOGIC AGENTS

89. Vaccines, Toxoids, and Serologic Agents 863

XX HEAVY METAL ANTAGONISTS, ENZYMES, AND MISCELLANEOUS AGENTS

90. Chelating Agents 885
91. Enzymes Used as Drugs 893
92. Miscellaneous Drugs 899

Manufacturers 908
Indexes
Adverse Reactions 913
Drugs 971
Calculation of Drug Dosage in Children ..... back cover

Usual Dosage	Preparations
Oral: Adults, initially, 1 or 2 mg 3 times daily; maintenance dose, 1 mg 2 times daily. *Children*, dosage not established. *Intramuscular, Intravenous, Subcutaneous: Adults*, 0.1 or 0.2 mg at 4-hour intervals 3 or 4 times daily. *Children*, dosage not established.	Tablets 1 and 2 mg Solution (for injection) 0.2 mg/ml in 1 and 5 ml containers
Oral: Adults, initially, 25 mg 4 times daily. Timed-release tablet, 50 mg 2 times daily; for nocturnal relief, 75 mg at bedtime. Maintenance dosage is adjusted to meet individual needs.	Tablets 25 mg Tablets (timed-release) 50 and 75 mg
Oral: Adults, 5 mg every 12 hours.	Tablets 5 mg
Oral: Adults, 25 mg 4 times daily. Dosage increased gradually to 50 mg if necessary.	Liquid 25 mg/5 ml Tablets 25 mg
Oral: Adults, intially, 50 to 100 mg every 6 hours; dose reduced to 25 mg for patients who cannot tolerate larger doses. Maintenance dose, generally one-half initial dose. *Children*, 6 mg/kg daily in 4 doses. *Intramuscular: Adults*, 50 mg every 6 hours. *Children*, 3 mg/kg in 4 doses.	Tablets 50 mg Powder (for injection) 50 mg
Oral: Adults, 10 mg twice daily; dose gradually increased to 50 mg if untoward effects do not appear.	Daricon: Tablets 10 mg Vio-Thene: Tablets (timed-release) 10 mg
Oral: Adults, 10 mg 4 times daily. *Children*, 0.8 mg/kg divided into 4 doses.	Tablets 5 mg
Oral: Adults, 10 or 20 mg 3 or 4 times daily; additional 10 mg may be required at bedtime. Some patients may require 30 mg 4 times daily.	Tablets 10 mg
Oral: Adults, 5 mg 4 times daily. An additional 5 mg may be required at bedtime. *Children*, dosage not established.	Tablets 5 mg

TABLE 1—ANTICHOLINERGIC ANTISPASMODICS (Cont'd.)

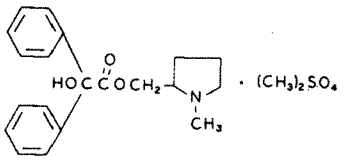
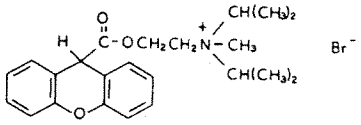
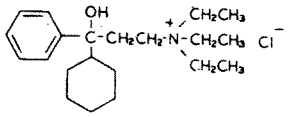
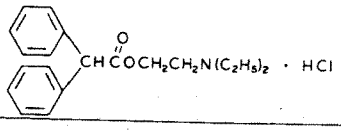
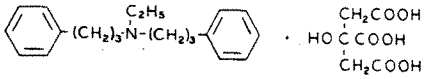
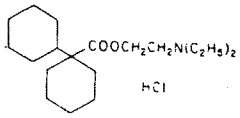
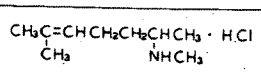
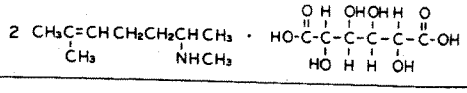
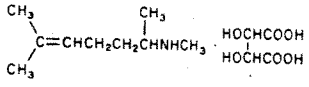
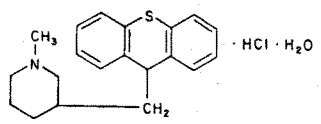
Drug	Chemical Structure	
Poldine Methylsulfate Nacton (McNeil)		*Oral: Ad* dosage n
Propantheline Bromide Pro-Banthine (Searle)		*Oral: Ad* timed-rel 1.5 mg, k *Intramus* (Powder injection
Tridihexethyl Chloride Pathilon (Lederle)		*Oral: Ad* bedtime. Alternati if necessa *Subcutan* 10 to 20

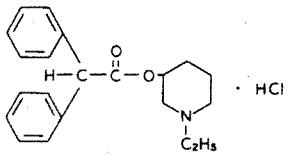
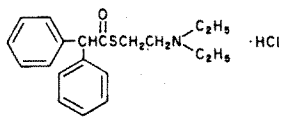
TABLE 2—OTHER SYNTHETIC ANTISPASMODICS

Drug	Chemical Structure	
Adiphenine Hydrochloride Trasentine Hydrochloride (Ciba) Drug also marketed under generic name.		*Oral: Adu* dosage no
Alverine Citrate Profenil (Smith, Miller & Patch) Spacolin (Philips Roxane		*Oral: Adu*
Dicyclomine Hydrochloride Bentyl (Merrell-National		*Oral, Intr* *Children,* times dail
Isometheptene Hydrochloride Octin Hydrochloride (Knoll) Drug also marketed under generic name.		*Intramusc* *Children,*
Isometheptene Mucate Octin Mucate (Knoll)		*Oral: Adul* not establi
Isometheptene Tartrate Isometene (Canfield)		*Intramuscu* *Children,* d
Methixene Hydrochloride Trest (Dorsey)		*Oral: Adult* necessary.

Usual Dosage	Preparations
Oral: Adults, 4 mg 3 or 4 times daily. *Children*, dosage not established.	Tablets 4 mg
Oral: Adults, 15 mg 3 times daily and 30 mg at bedtime, or timed-release preparation given 2 or 3 times daily. *Children*, 1.5 mg/kg daily in 4 doses. *Intramuscular, Intravenous: Adults*, 30 mg every 6 hours. (Powder dissolved in not less than 10 ml of sodium chloride injection for intravenous administration.)	Tablets 7.5 and 15 mg Tablets (timed-release) 30 mg Powder (for injection) 30 mg
Oral: Adults, 25 mg 3 times daily before meals and 50 mg at bedtime. Dosage increased to 50 mg 4 times daily if necessary. Alternatively, timed-release preparation given every 12 hours; if necessary, this dose is given every 6 hours. *Subcutaneous, Intravenous, Intramuscular: Adults*, 10 to 20 mg every 6 hours.	Capsules (timed-release) 75 mg Tablets 25 mg Solution (for injection) 10 mg/ml in 1 ml containers

Usual Dosage	Preparations
Oral: Adults, 75 to 150 mg 3 times daily. *Children*, dosage not established.	Tablets 75 mg
Oral: Adults, 120 mg 1 to 3 times daily.	Tablets 120 mg
Oral, Intramuscular: Adults, 10 to 20 mg 3 or 4 times daily. *Children*, 10 mg 3 or 4 times daily. *Infants*, 5 mg 3 or 4 times daily.	Capsules 10 mg Syrup 10 mg/5 ml Tablets 20 mg Solution (for injection) 10 mg/ml in 2 and 10 ml containers
Intramuscular: Adults, 100 mg repeated once in 4 to 6 hours. *Children*, dosage not established.	Solution (for injection) 100 mg/ml in 1 ml containers
Oral: Adults, 130 mg 3 or 4 times daily. *Children*, dosage not established.	Tablets 130 mg
Intramuscular: Adults, 100 mg repeated once in 4 to 6 hours. *Children*, dosage not established.	Solution (for injection) 100 mg/ml in 10 ml containers
Oral: Adults, 1 mg 3 times daily. Dose increased to 2 mg if necessary. *Children*, dosage not established.	Tablets 1 mg

TABLE 2—OTHER SYNTHETIC ANTISPASMODICS (Cont'd.)

Drug	Chemical Structure
Piperidolate Hydrochloride Dactil (Lakeside)	
Thiphenamil Hydrochloride Trocinate (Poythress)	

Belbarb (Arnar-Stone): Each tablet contains scopolamine hydrobromide 0.0072 mg, atropine sulfate 0.024 mg, hyoscyamine hydrobromide 0.128 mg, and phenobarbital 16 mg; each No. 2 tablet contains scopolamine hydrobromide 0.0072 mg, atropine sulfate 0.024 mg, hyoscyamine hydrobromide 0.128 mg, and phenobarbital 32 mg.

Belladenal (Sandoz): Each tablet or timed-release tablet contains levorotatory alkaloids of belladonna 0.25 mg and phenobarbital 50 mg; each 5 ml of elixir contains levorotatory alkaloids of belladonna 0.078 mg and phenobarbital 15.6 mg.

Bellergal (Sandoz): Each tablet contains levorotatory alkaloids of belladonna 0.1 mg, ergotamine tartrate 0.3 mg, and phenobarbital 20 mg; each timed-release tablet contains levorotatory alkaloids of belladonna 0.2 mg, ergotamine tartrate 0.6 mg, and phenobarbital 40 mg.

Bentyl W/Phenobarbital (Merrell-National): Each capsule, tablet, or 5 ml of syrup contains dicyclomine hydrochloride 10 mg and phenobarbital 15 mg.

Butibel (McNeil): Each tablet or 5 ml of elixir contains belladonna extract 15 mg and butabarbital sodium 15 mg; each timed-release tablet contains belladonna extract 30 mg and butabarbital sodium 30 mg.

Cantil W/Phenobarbital (Lakeside): Each tablet contains mepenzolate bromide 25 mg and phenobarbital 16 mg.

Chardonna (Rorer): Each tablet contains belladonna extract 5 mg, activated charcoal 60 mg, and phenobarbital 20 mg.

Combid (Smith Kline & French): Each timed-release capsule contains isopropamide iodide 5 mg and prochlorperazine maleate 10 mg.

Daricon-PB (Beecham-Massengill): Each tablet contains oxyphencyclimine hydrochloride 5 mg and phenobarbital 15 mg.

Donnalate (Robins): Each tablet contains hyoscyamine sulfate 0.052 mg, atropine sulfate 0.01 mg, scopolamine hydrobromide 0.003 mg, dihydroxyaluminum aminoacetate 500 mg, and phenobarbital 8.1 mg.

Donnatal (Robins): Each capsule, tablet, or 5 ml of elixir contains hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, scopolamine hydrobromide 0.0065 mg, and phenobarbital 16.2 mg; each No. 2 tablet contains same formulation as Donnatal except phenobarbital 32.4 mg; each timed-release tablet contains hyoscyamine sulfate 0.3111 mg, atropine sulfate 0.0582 mg, scopolamine hydrobromide 0.0195 mg, and phenobarbital 48.6 mg.

Donphen (Lemmon): Each tablet contains hyoscyamine sulfate 0.1 mg, atropine sulfate 0.02 mg, scopolamine hydrobromide 6 μg, and phenobarbital 15 mg.

Enarax (Roerig): Each tablet contains oxyphencyclimine hydrochloride 5 or 10 mg and hydroxyzine hydrochloride 25 mg.

Hybephen (Beecham-Massengill): Each tablet or 5 ml of elixir contains hyoscyamine sulfate 0.1277 mg, atropine sulfate 0.0233 mg, scopolamine hydrobromide 0.0094 mg, and phenobarbital 15 mg.

Kinesed (Stuart): Each chewable tablet contains hyoscyamine sulfate 0.1 mg, atropine sulfate 0.02 mg, scopolamine hydrobromide 0.007 mg, simethicone 40 mg, and phenobarbital 16 mg.

Kolantyl (Merrell-National): Each tablet contains dicyclomine hydrochloride 5 mg, dried aluminum hydroxide gel 300 mg, magnesium oxide 185 mg, and methylcellulose 100 mg; each 5 ml of gel contains dicyclomine hydrochloride 2.5 mg, aluminum hydroxide 150 mg, magnesium hydroxide 150 mg, and methylcellulose 50 mg; each wafer contains dicyclomine hydrochloride 2.5 mg, dried aluminum hydroxide gel 180 mg, magnesium hydroxide 170 mg, and methylcellulose 50 mg.

Usual Dosage	Preparations
Oral: Adults, 50 mg 4 times daily. *Children*, dosage not established.	Tablets 50 mg
Oral: Adults, initially, 400 mg every 4 hours. *Children over 6 years*, 200 mg every 4 hours. Dose given less frequently after symptoms are controlled.	Tablets 100 and 400 mg

Levsin W/Phenobarbital (Kremers-Urban): Each tablet or 5 ml of elixir contains hyoscyamine sulfate 0.125 mg and phenobarbital 15 mg; each milliliter of injection contains hyoscyamine sulfate 0.25 mg and phenobarbital 15 mg.

Milpath (Wallace): Each tablet contains tridihexethyl chloride 25 mg and meprobamate 200 or 400 mg.

Pamine PB (Upjohn): Each tablet contains methscopolamine bromide 2.5 mg and phenobarbital 15 mg; each half-strength tablet or 5 ml of elixir contains methscopolamine bromide 1.25 mg and phenobarbital 8 mg; each milliliter of drops contains methscopolamine bromide 0.5 mg and phenobarbital 20 mg.

Pathibamate (Lederle): Each tablet contains tridihexethyl chloride 25 mg and meprobamate 200 or 400 mg.

Pathilon W/Phenobarbital (Lederle): Each tablet contains tridihexethyl chloride 25 mg and phenobarbital 15 mg; each timed-release tablet contains tridihexethyl chloride 75 mg and phenobarbital 45 mg.

Phenobarbital and Belladonna (Upjohn): Each tablet contains belladonna extract 8.1 mg and phenobarbital 16.2 or 32.4 mg.

Pro-Banthine W/Dartal (Searle): Each tablet contains propantheline bromide 15 mg and thiopropazate dihydrochloride 5 mg.

Pro-Banthine W/Phenobarbital (Searle): Each tablet contains propantheline bromide 15 mg and phenobarbital 15 mg.

Prydonnal (Smith Kline & French): Each timed-release capsule contains belladonna alkaloids 0.4 mg and phenobarbital 65 mg.

Robinul-PH (Robins): Each tablet contains glycopyrrolate 1 or 2 mg and phenobarbital 16.2 mg.

Sidonna (Reed & Carnrick): Each tablet contains simethicone 25 mg, hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, scopolamine hydrobromide 0.0065 mg, and butabarbital sodium 16 mg.

Trasentine-Phenobarbital (Ciba): Each tablet contains adiphenine hydrochloride 50 mg and phenobarbital 20 mg.

Valpin-PB (Endo): Each tablet or 5 ml of elixir contains anisotropine methylbromide 10 mg and phenobarbital 8 mg.

Chapter 79

ANTACIDS

Antacids are used to reduce gastric acidity in the symptomatic treatment of peptic ulcer, hyperchlorhydria, gastritis, and other disorders of the stomach and duodenum. There is no conclusive evidence that they hasten the healing of peptic ulcers or reduce the number of relapses, but they are effective in relieving pain when adequate doses are given at sufficiently frequent intervals.

The goal of antacid therapy is to raise the pH of the gastric contents to 5; at this level the damaging effects of acidity are greatly reduced and the proteolytic activity of pepsin is almost completely abolished. In addition to a high neutralizing capacity, the ideal antacid should have a prolonged duration of action and should not cause untoward systemic or local effects. These goals are difficult, if not impossible, to attain. The duration of action is limited by the emptying time of the stomach, and prolonged neutralization requires frequent drug administration. Compounds with low toxicity have little neutralizing capacity, while the potent antacids can cause severe systemic effects. Alterations in normal bowel function usually occur during antacid therapy. Other undesired local effects of some agents are release of carbon dioxide in the stomach and interference with the absorption of other drugs.

Although sodium bicarbonate is highly soluble and has an immediate and pronounced neutralizing effect, its duration of action is very brief, it releases carbon dioxide in the stomach and it produces metabolic alkalosis in some patients. Therefore, sodium bicarbonate has little merit as a gastric antacid.

Calcium carbonate is a highly effective antacid because of its rapid onset of action, high neutralizing capacity, and relatively prolonged action. The pH of the gastric contents can be maintained above 4 by hourly administration of 4 g of calcium carbonate, and the presence of food in the stomach will prolong its action. Calcium carbonate is reconstituted in the intestine or insoluble calcium soaps or calcium phosphate are formed; however, significant amounts of calcium may be absorbed by some patients (see Adverse Reactions and Precautions). Tribasic calcium phosphate also has been used as a gastric antacid, but its neutralizing capacity is less than that of calcium carbonate.

Aluminum hydroxide is a nonabsorbable antacid with demulcent, adsorbent, and astringent properties. It has a slow onset of action and a low neutralizing capacity, but there is no evidence that it is less effective in relieving pain than other more potent antacids. The symptomatic relief obtained may be due to the drug's demulcent action or to other properties unrelated to reduction of acidity. Aluminum hydroxide does not produce systemic effects because insoluble compounds are formed in the intestine (eg, aluminum phosphate). Since the elimination of phosphate in the feces results in a compensatory decrease in the urinary excretion of phosphate, it may be used to treat phosphatic renal calculi; however, basic aluminum carbonate is considered more effective for this purpose. Other aluminum products used as antacids are aluminum phosphate, dihydroxyaluminum aminoacetate [Robalate], and dihydroxyaluminum sodium carbonate. These compounds have properties similar to those of aluminum hydroxide; however, aluminum phosphate does not increase the fecal elimination of phosphate.

Magnesium hydroxide, usually in the form of milk of magnesia, has a rapid and relatively long neutralizing action. Insoluble magnesium compounds are formed in the intestine, but some magnesium ions may be absorbed.

Magnesium carbonate and magnesium oxide also have a high neutralizing capacity, but tribasic magnesium phosphate and magnesium trisilicate are relatively weak antacids. Magaldrate [Riopan] is a chemical union of magnesium and aluminum hydroxides.

Several other drugs have been used to reduce gastric acidity. Resins, such as polyamine-methylene resin [Resinat], have a slight neutralizing effect but are bulky and unpalatable. Insoluble bismuth salts, gastric mucin, methylcellulose, and glycine are common ingredients of mixtures, but their therapeutic value is doubtful.

Adverse Reactions and Precautions

The most common adverse reactions associated with prolonged use of antacids are constipation or diarrhea. Because of the cathartic effects of the magnesium salts, large and frequent doses often cannot be tolerated. Constipation may result from repeated administration of calcium or aluminum preparations; formation of fecal concretions is an occasional complication. Disruption of normal bowel function can be minimized by the use of magnesium salts with calcium or aluminum preparations.

The presence of an antacid in the stomach causes a compensatory increase in the secretion of gastric juice and in the output of hydrochloric acid. There is no convincing evidence that the increased secretion rate outlasts the neutralizing effect of any antacid except possibly calcium carbonate. Rebound gastric hypersecretion has been demonstrated several hours after administration of this antacid. The acid rebound has been variously attributed to a local effect of the calcium ion, to hypercalcemia, or to the superior neutralizing capacity of calcium carbonate. The clinical significance of this phenomenon is unclear. In treating peptic ulcer, the rebound hypersecretion would be buffered by additional doses of the antacid and by frequent feeding. However, it has been suggested that sustained, buffered hypersecretion could lead to hyperplasia of the parietal cells.

The milk-alkali syndrome (Burnett syndrome) is an occasional complication that occurs after the prolonged administration of large doses of sodium bicarbonate or calcium carbonate together with the ingestion of foods containing vitamin D, such as milk. The essential features of this syndrome are hypercalcemia and renal insufficiency with azotemia and metastatic calcinosis. Hematologic findings usually include normal or elevated phosphorus levels, normal alkaline phosphatase levels, and mild metabolic alkalosis. The urinary excretion of calcium is generally not increased. Conjunctival deposition of calcium can occur, manifested by band keratopathy. Nausea is a common symptom. Predisposing factors are preexisting renal disease, hypertension, gastrointestinal hemorrhage, and dehydration and electrolyte imbalance due to excessive vomiting or aspiration of the gastric contents. Magnesium and aluminum salts have not been implicated in this syndrome. Sodium bicarbonate may cause pronounced metabolic alkalosis in patients with impaired renal function.

Antacids containing magnesium can produce severe toxic effects in patients with impaired renal function. The symptoms of magnesium poisoning include lethargy, coma, circulatory failure, and respiratory arrest due to neuromuscular blockade.

Sodium bicarbonate is contraindicated in patients on a low-sodium diet, and some other antacids contain sufficient sodium to preclude their unrestricted use in these patients. Information is not available for all antacids, but chemical analysis has shown that aluminum preparations may contain significant amounts of sodium, although there is considerable variation in products from different manufacturers. Milk of magnesia (magnesium hydroxide) and calcium carbonate, U.S.P., have a relatively low sodium content.

Eructation and flatulence may occur after the administration of carbonates or bicarbonate due to the release of carbon dioxide in the stomach. The gastric distention produced by the carbon dioxide could cause perforation of a gastric ulcer.

Aluminum salts occasionally cause nausea and vomiting. Phosphate deficiency and osteomalacia may develop in patients with a low phosphate intake during prolonged administration of large doses of aluminum preparations, with the exception of aluminum phosphate.

INDIVIDUAL EVALUATIONS

SODIUM BICARBONATE

Sodium bicarbonate is a highly soluble antacid with an immediate and pronounced neutralizing effect; however, it is not a satisfactory antacid because of its brief duration

of action and occasional untoward effects.

Adverse reactions include eructation and flatulence, sodium retention, metabolic alkalosis, and the milk-alkali syndrome (see the Introductory Statement).

For other uses, see Chapter 16, Replenishers and Regulators of Water, Electrolytes, and Nutrients.

USUAL DOSAGE.—This agent has little merit as a gastric antacid because of the reasons stated above. The U.S.P. dosage is: *Oral: Adults,* 300 mg to 2 g one to four times daily.

PREPARATIONS.—Sodium Bicarbonate, U.S.P. Drug marketed under generic name.

CALCIUM CARBONATE

Calcium carbonate is regarded by some authorities as the antacid of choice. The powder form has a rapid onset of action, high neutralizing capacity, and relatively prolonged action. The tablets are less effective.

Constipation and lack of palatability are frequent complaints; fecal concretions may occur. The constipating effects of this drug can be minimized by combined therapy with magnesium salts. A mixture of two parts magnesium oxide and one part calcium carbonate will not affect the bowel function of most patients. If constipation or diarrhea does occur, the ratio of the ingredients may be adjusted. Patients receiving prolonged calcium carbonate therapy together with foods containing vitamin D may develop the milk-alkali syndrome; other adverse effects are hypercalcemia and rebound hyperacidity. Liberation of carbon dioxide in the stomach may cause eructation and flatulence.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults,* 1 to 4 g with water four or more times daily; to control severe symptoms, 2 to 4 g every hour may be required. The tablets should be chewed before swallowing.

PREPARATIONS.—Calcium Carbonate, U.S.P. *Oral:* Powder (precipitated); tablets 600 mg.

AVAILABLE TRADEMARKS.—Glycate (Durst): Each chewable tablet contains calcium carbonate 300 mg and glycine 150 mg.

Titralac (Riker): Each 5 ml of liquid contains calcium carbonate 1 g and glycine 300 mg; each tablet contains calcium carbonate 420 mg and glycine 180 mg.

Drug also marketed under generic name.

CALCIUM PHOSPHATE, TRIBASIC

This agent is occasionally used as an antacid, but it has only a mild and brief neutralizing action. Tribasic calcium phosphate is also used as a source of calcium and phosphate in deficiency states (see Chapter 17, Blood Calcium Regulators).

For adverse reactions, see the Introductory Statement.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults,* 1 to 4 g with water three or more times daily; to control severe symptoms, 2 to 4 g every hour may be required.

PREPARATIONS.—Calcium Phosphate, Tribasic, N.F. *Oral:* Powder. Drug marketed under generic name.

ALUMINUM HYDROXIDE GEL [Amphojel]
DRIED ALUMINUM HYDROXIDE GEL
[Amphojel Tablets]

Aluminum hydroxide gel is a nonabsorbable antacid with demulcent, adsorbent, and astringent properties. It has a slow onset of action and a low neutralizing capacity. Different preparations of aluminum hydroxide vary in neutralizing potency; tablets are less effective than liquid preparations. The drug increases phosphate excretion in the feces and sometimes is used in the treatment of phosphatic renal calculi.

Aluminum hydroxide is relatively nontoxic; the most common adverse reaction is constipation, which can be controlled by combined therapy with a magnesium compound. Fecal concretions may occur. The astringent action of this agent occasionally causes nausea and vomiting. If phosphate intake is low, patients receiving large doses for long periods may develop hypophosphatemia and osteomalacia. Aluminum hydroxide can interfere with the absorption of other drugs and should not be given simultaneously with such agents as anticholinergics and barbiturates. Aluminum hydroxide preparations contain sodium and should not be administered to patients on a low-sodium diet.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults,* 5 to 10 ml of gel or tablets containing 300 or 600 mg given with water four times daily; tablets should be chewed before swallowing. To control severe symptoms, 40 ml

of gel every hour may be required; this may be given by intragastric drip after dilution with two to three parts water. In the treatment of phosphatic renal calculi, 40 ml of gel is given after meals and at bedtime; in most patients, this dose will reduce the urinary excretion of phosphate within a few days.

PREPARATIONS.—Amphojel (Wyeth). *Oral:* Suspension (gel); tablets 300 and 600 mg (dried gel). Forms also marketed under generic name.

ADDITIONAL TRADEMARKS.— Aluminum Hydroxide Gel: Co-Lu-Gel (Ulmer). Dried Aluminum Hydroxide Gel: Algelum (Robinson).

ALUMINUM PHOSPHATE GEL [Phosphaljel]

This nonabsorbable liquid preparation has properties similar to aluminum hydroxide. It is regenerated in the intestine and endogenous phosphate is spared; therefore, it should be used in preference to aluminum hydroxide when a high phosphate diet cannot be maintained.

For adverse reactions, see the Introductory Statement.

USUAL DOSAGE.—*Oral:* Dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults*, 15 to 45 ml with water four or more times daily.

PREPARATIONS.—Phosphaljel (Wyeth). *Oral:* Suspension 4%.

DIHYDROXYALUMINUM AMINOACETATE [Robalate]

This agent is a nonabsorbable antacid with properties similar to aluminum hydroxide. In the dried form, dihydroxyaluminum aminoacetate has a greater neutralizing capacity than dried aluminum hydroxide gel, but comparison of liquid preparations has shown that aluminum hydroxide gel is more effective. There is little evidence to support the claim that dihydroxyaluminum aminoacetate is less constipating than aluminum hydroxide.

For adverse reactions, see the Introductory Statement.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults*, 500 mg to 2 g with water four or more times daily.

PREPARATIONS.—Robalate (Robins). *Oral:* Suspension 500 mg/5 ml; tablets 500 mg.

ADDITIONAL TRADEMARKS.—Alglyn (Brayten), Alkam (First Texas), Alzinox (Cooper).

Other Aluminum Preparations

Basic Aluminum Carbonate [Basaljel (Wyeth)]

Dihydroxyaluminum Sodium Carbonate [Rolaids (American Chicle)]

MAGNESIUM HYDROXIDE
MAGNESIUM OXIDE
MILK OF MAGNESIA

These antacids have the same properties because magnesium oxide is converted to the hydroxide in water. Milk of magnesia, a suspension of magnesium hydroxide, is used mainly as a laxative. These preparations have a rapid onset of action and a high neutralizing capacity. Their duration of action is longer than that of sodium bicarbonate.

The most common untoward effect is diarrhea; this can be minimized by combined therapy with a calcium or aluminum preparation. Absorbed magnesium may produce toxic effects in patients with impaired renal function (see the Introductory Statement).

For other uses of these preparations, see Chapter 81, Laxatives and Agents Affecting Fecal Consistency.

USUAL DOSAGE.—The dose and frequency of administration depend upon the severity of symptoms and relief obtained.

Magnesium Hydroxide:

Oral: Adults, 300 to 600 mg of powder or one or two tablets with water four or more times daily; *children*, one-half or one tablet. Tablets should be chewed before swallowing.

Magnesium Oxide:

Oral: Adults, 250 mg to 1.5 g with water four or more times daily.

Milk of Magnesia:

Oral: Adults, 5 ml of liquid four or more times daily; *children*, 2.5 to 5 ml of liquid.

PREPARATIONS.—

Magnesium Hydroxide, N.F. *Oral:* Powder; tablets 300 mg.

Magnesium Oxide, U.S.P. *Oral:* Capsules and powder available in both heavy and light form (light form suspends more readily in liquids).

Milk of Magnesia, U.S.P. *Oral:* Suspension.

Drugs marketed under generic name.

MAGNESIUM CARBONATE

This alkaline salt is similar to magnesium hydroxide and magnesium oxide, but differs from these agents in that carbon dioxide is

liberated in the stomach during neutralization. Magnesium carbonate has a high neutralizing capacity and is a common ingredient in antacid mixtures.

For adverse reactions and precautions, see the Introductory Statement. For other uses, see Chapter 81, Laxatives and Agents Affecting Fecal Consistency.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults*, 500 mg to 2 g with water four times daily; to control severe symptoms, 2 g each hour may be required. Tablets should be chewed before swallowing.

PREPARATIONS.—Magnesium Carbonate, N.F. *Oral:* Powder; tablets 2 g. Drug marketed under generic name.

MAGNESIUM PHOSPHATE, TRIBASIC

The actions of this alkaline powder are similar to those of other magnesium preparations. Its neutralizing capacity is less than that of magnesium carbonate but greater than that of magnesium trisilicate.

For adverse reactions and precautions, see the Introductory Statement.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults*, 1 to 2 g with water four times daily; to control severe symptoms, 2 g every hour may be required.

PREPARATIONS.—Tribasic Magnesium Phosphate, N.F. *Oral:* Powder. Drug marketed under generic name.

MAGNESIUM TRISILICATE

Magnesium trisilicate has a slow onset of action and low neutralizing capacity. It is a common ingredient of many antacid mixtures. Magnesium trisilicate reacts with hydrochloric acid to form hydrated silicon dioxide which may provide symptomatic relief by coating the crater of an ulcer. It also has adsorbent properties.

For adverse reactions and precautions, see the Introductory Statement.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults*, 1 to 4 g with water four times daily; to control severe symptoms, 2 g or more every hour may be required. Tablets should be chewed before swallowing.

PREPARATIONS.—Magnesium Trisilicate, U.S.P. *Oral:* Powder; tablets 300 and 500 mg.

AVAILABLE TRADEMARK.—Trisomin (Lilly). Drug also marketed under generic name.

MAGALDRATE [Riopan]

Magaldrate is a chemical union of aluminum and magnesium hydroxides. It has a low sodium content.

Prolonged use may cause constipation in some patients. Although some limited absorption might occur, magaldrate is unlikely to cause disturbances of acid-base balance. However, even limited absorption may produce hypermagnesemia in patients with impaired renal function. For other adverse reactions and precautions, see the Introductory Statement.

USUAL DOSAGE.—*Oral:* The dose and frequency of administration depend upon the severity of symptoms and relief obtained. *Adults*, 400 to 800 mg four or more times daily. Hourly administration may be necessary to control severe symptoms.

PREPARATIONS.—Riopan (Ayerst). *Oral:* Suspension 400 mg/5 ml; tablets 400 mg; tablets (chewable) 400 mg.

MIXTURES

Disruption of normal bowel function after prolonged administration of antacids can be minimized by alternating magnesium salts with calcium or aluminum preparations or by using mixtures. Some combination products contain additional ingredients of doubtful therapeutic value, such as gastric mucin, methylcellulose, glycine, simethicone, and oxethazaine. Preparations containing antacids combined with anticholinergics and barbiturates should not be used because the dose of each of these agents should be adjusted individually and because some antacids, such as aluminum hydroxide, may interfere with the absorption of other drugs (for a listing of these mixtures, see Chapter 78, Antispasmodics).

The dose and frequency of administration depend upon the severity of symptoms and relief obtained.

Mixtures Containing Aluminum Hydroxide and Magnesium Salts

Aludrox (Wyeth): Tablets and suspension containing aluminum and magnesium hydroxides.

A-M-T (Wyeth): Tablets and suspension containing dried aluminum hydroxide gel and magnesium trisilicate.

Bidrox (McNeil): Each 5 ml of suspension contains

aluminum hydroxide 400 mg and magnesium hydroxide 100 mg.

Cimadrox (Beecham-Massengill): Each tablet contains dried aluminum hydroxide gel 200 mg, magnesium trisilicate 400 mg, and ascorbic acid 20 mg.

Creamalin (Winthrop): Each tablet or 5 ml of suspension contains aluminum hydroxide gel 320 mg and magnesium hydroxide 75 mg.

Delcid (Merrell-National): Each 5 ml of liquid contains aluminum hydroxide gel 600 mg and magnesium hydroxide 665 mg.

Gaviscon (Marion): Each tablet contains dried aluminum hydroxide gel 80 mg, magnesium trisilicate 20 mg, sodium bicarbonate 70 mg, and alginic acid 200 mg.

Gelusil (Warner-Chilcott): Each tablet or 4 ml of liquid contains aluminum hydroxide 250 mg and magnesium trisilicate 500 mg.

Gelusil-M (Warner-Chilcott): Each tablet or 5 ml of suspension contains aluminum hydroxide 250 mg, magnesium hydroxide 100 mg, and magnesium trisilicate 500 mg.

Maalox (Rorer): Each 5 ml of suspension or No. 1 tablet contains combined hydroxides of aluminum and magnesium 400 mg; each No. 2 tablet contains combined hydroxides of aluminum and magnesium 800 mg.

Malcogel (Upjohn): Each 5 ml of liquid contains aluminum hydroxide 300 mg and magnesium trisilicate 600 mg.

Malcotabs (Upjohn): Each tablet contains dried aluminum hydroxide gel 600 mg and magnesium trisilicate 300 mg.

Mucotin (Warner-Chilcott): Each tablet contains dried aluminum hydroxide gel 250 mg, magnesium hydroxide 65 mg, magnesium trisilicate 450 mg, and gastric mucin 65 mg.

Mylanta (Stuart): Each tablet or 5 ml of liquid contains aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg.

Neosorb (Lemmon): Each tablet contains aluminum hydroxide gel 250 mg, magnesium trisilicate 460 mg, and methylcellulose 65 mg.

Neosorb Plus (Lemmon): Suspension containing aluminum hydroxide 6%, magnesium hydroxide 3%, and magnesium trisilicate 3%; each tablet contains dried aluminum hydroxide gel 300 mg, magnesium hydroxide 150 mg, and magnesium trisilicate 150 mg.

Neutralox (Lemmon): Each tablet or 5 ml of liquid contains dried aluminum hydroxide gel 300 mg, magnesium hydroxide 150 mg, and magnesium trisilicate 150 mg.

Oxaine-M (Wyeth): Each 5 ml of suspension contains oxethazaine 10 mg in alumina gel with magnesium hydroxide.

Silain-Gel Liquid (Robins): Each 5 ml of liquid contains aluminum hydroxide 282 mg, magnesium hydroxide 85 mg, and simethicone 25 mg.

Silain-Gel Tablets (Robins): Each tablet contains aluminum hydroxide-magnesium carbonate 282 mg, magnesium hydroxide 85 mg, and simethicone 25 mg.

Trigelma (Durst): Each tablet contains aluminum hydroxide gel 250 mg, magnesium hydroxide 60 mg, and magnesium trisilicate 150 mg; each 5 ml of liquid contains aluminum hydroxide gel 2.1 g and magnesium hydroxide paste 300 mg.

Trisogel (Lilly): Each capsule contains aluminum hydroxide gel 100 mg and magnesium trisilicate 280 mg; each 5 ml of liquid contains aluminum hydroxide 140 mg and magnesium trisilicate 540 mg.

WinGel (Winthrop): Each tablet or 5 ml of liquid contains aluminum and magnesium hydroxides 410 mg stabilized with hexitol.

Mixtures Containing Calcium Carbonate and Other Antacids

Alkets (Upjohn): Each tablet contains calcium carbonate 750 mg, magnesium carbonate 120 mg, and magnesium oxide 60 mg.

Buffertabs (Durst): Each tablet contains calcium carbonate 200 mg, magnesium carbonate 120 mg, bismuth subcarbonate 60 mg, aluminum hydroxide 30 mg, and aminoacetic acid 50 mg.

Camalox (Rorer): Each 5 ml of suspension contains calcium carbonate 250 mg, aluminum hydroxide 225 mg, and magnesium hydroxide 200 mg.

Dicarbosil (Arch): Each tablet contains calcium carbonate 489 mg, magnesium carbonate 10 mg, and magnesium trisilicate 6 mg.

Ducon (Smith Kline & French): Each 5 ml of suspension contains calcium carbonate 375 mg, aluminum hydroxide 720 mg, and magnesium hydroxide 350 mg.

Ratio (Warren-Teed): Each tablet contains calcium carbonate 400 mg and magnesium carbonate 50 mg.

Tums (Lewis-Howe): Each tablet contains calcium carbonate 489 mg, magnesium carbonate 10 mg, and magnesium trisilicate 6 mg.

Chapter 80

ANTIDIARRHEALS

Diarrhea is a pathologic acute or chronic increase in the fluidity and frequency of the stools. This symptom may be caused by infection (bacterial, viral, fungal, or parasitic), poisoning (eg, heavy metals, pesticides, bacterial exotoxins), drugs, altered distribution of bile acids, malabsorption, allergy, ischemia, hypermotility, and gastrointestinal lesions, including inflammatory conditions (regional enteritis) and hormone-producing neoplasms (eg, carcinoid).

Many of the drugs discussed in this chapter are nonspecific and useful only for the symptomatic treatment of diarrhea. They include drugs of demonstrated effectiveness (eg, diphenoxylate hydrochloride with atropine [Lomotil], opium tincture), as well as other agents (eg, bismuth subcarbonate, kaolin, pectin) whose supposed effectiveness is supported mainly by tradition. Drugs of the latter group are generally available only as components of mixtures, and until well-controlled clinical studies are available, generally no recommendation is made for these agents.

The specific cause of acute, self-limiting diarrhea often remains unknown. A bacterial toxin is the most common cause in children; viruses also may be responsible. The nonspecific antidiarrheal agents may be useful in mitigating the symptoms of acute diarrhea (eg, opiates in the treatment of *Salmonella* food poisoning). The symptomatic treatment of chronic diarrhea is justified only to give the patient relief while a search is made for the cause or when symptomatic therapy is needed in addition to treatment of the underlying cause.

The drugs used for specific treatment of the various underlying causes of diarrhea include antibacterial agents (eg, neomycin), antiprotozoal agents (eg, metronidazole [Flagyl]), and cholestyramine resin [Cuemid, Questran]. Other drugs useful for the specific treatment of enteric infections resulting in diarrhea (eg, ampicillin, tetracycline, nystatin) are discussed in their respective chapters. These drugs should be used only when there is an established diagnosis or strong presumptive evidence of such a diagnosis and appropriate laboratory service for confirmation is not available. For example, in acute bacterial diarrhea of infants, a bacteriologic diagnostic service is not always available, and antibacterial therapy with an appropriate drug may be initiated on the basis of a careful, informed clinical diagnosis (enteropathogenic serotypes of *Escherichia coli* are the most common etiologic agents).

In any patient with severe diarrhea lasting more than 24 to 48 hours, fluid and electrolyte imbalances should be corrected to avoid dehydration and hypokalemia. In chronic diarrhea, electrolyte and nutrient status should be monitored and appropriate replacement therapy (eg, potassium, magnesium, calcium, albumin, vitamins) given when indicated. A careful investigation should be made to determine the cause of any persisting or continually recurring diarrhea and appropriate specific therapeutic measures (eg, medication, surgery, diet) should be instituted. Many such patients have special problems outside the scope of this book (eg, lactase deficiency, food allergies, carcinoid).

Nonspecific Antidiarrheals: The opiates are the most effective and prompt-acting nonspecific antidiarrheal agents. They act directly on intestinal smooth muscle to produce spasm with decreased peristalsis and increased segmentation. By tradition, the opium preparations, opium tincture and paregoric, are more widely used than the pure alkaloids, but

morphine and codeine are equally effective. Paregoric (camphorated opium tincture), which has been characterized as needlessly complex, nevertheless may have an advantage over opium tincture in its more convenient dosage. Since the usual oral doses of these preparations are neither euphoric nor analgesic, they can be used to treat acute, self-limited diarrhea with no risk of producing dependence; there is a real but slight risk of producing physical dependence if opiates are used to treat chronic diarrhea such as that associated with regional enteritis, colitis, or a colostomy. The effectiveness of diphenoxylate with atropine is about the same as that of the opium extracts. The mixture is classified as a Schedule V substance.

Theoretically, anticholinergic-type antispasmodics should be ideal antidiarrheals; however, it usually is not possible to give effective doses of these agents without producing undesirable reactions, since no drug of this class has been shown to exert a selective effect on the gastrointestinal tract. Ordinarily, there is no justification for adding a fraction of the usual clinical dose of an antispasmodic to an effective antidiarrheal agent. Anticholinergics are prescribed by many physicians when diarrhea is a problem in the irritable colon syndrome.

The use of the three bismuth salts (subcarbonate, subgallate, and subnitrate) as antidiarrheals is supported chiefly by tradition. Supposedly they adsorb toxins, bacteria, and viruses and provide a protective coating for the intestinal mucosa, but none of these conjectural actions has been substantiated.

Activated charcoal, once popular as an adsorbent in the treatment of diarrhea, is now used only for the treatment of poisonings, especially those caused by alkaloids, mercuric chloride, aspirin, or iron.

Kaolin and other hydrated aluminum silicate clays (eg, activated attapulgite) and pectin act as adsorbents and protectants. They are customarily available in preparations combining the two. Adequately controlled clinical studies demonstrating the efficacy of these popular but minimally effective antidiarrheal mixtures are lacking, and the usefulness of these agents is supported mainly by tradition. Frequently other ingredients are also present in the mixture.

Polycarbophil is a hydrophilic polyacrylic resin that may be effective in the symptomatic treatment of diarrhea because of its water-binding capacity; it is available only as an ingredient in mixtures.

Viable *Lactobacillus* cultures [Bacid, Lactinex] have been advocated for the treatment of diarrhea due to abnormal intestinal flora, especially for the rather common diarrhea that may occur postoperatively in a patient whose gut has been recolonized (eg, by staphylococci, *Candida*) after "sterilization" by antibacterial agents given in conjunction with gastrointestinal surgery. No well-controlled studies supporting the use of these preparations have been published.

Two amebicides, iodochlorhydroxyquin [Entero-Vioform] and diiodohydroxyquin [Diodoquin, Yodoxin], have been used in the prophylaxis of "traveler's diarrhea"; however, the cause of this diarrhea is not known and the efficacy of these drugs for this use has not been proved. (See Chapter 62, Amebicides.)

Drugs Having Specific Indications: Although furazolidone [Furoxone] is useful in the treatment of symptomatic giardiasis, metronidazole [Flagyl] and quinacrine hydrochloride [Atabrine] are more effective. Metronidazole also is useful in the treatment of intestinal amebiasis (see Chapter 62, Amebicides).

Mild candidal superinfections may respond to cessation of antibacterial therapy. In severe superinfections with penicillinase-producing staphylococci, the broad-spectrum antibiotics should be stopped and treatment should include vancomycin [Vancocin] orally, a penicillinase-resistant penicillin or a cephalosporin parenterally, and measures to combat shock.

Acute gastroenteritis due to *Salmonella* infections other than typhoid fever ordinarily should not be treated with antibacterial agents because there is evidence that antibiotics do not shorten the period of illness and may prolong the excretion of organisms. However, antibiotic therapy is advisable in severe cases, especially in patients who are vulnerable to serious illness and death (eg, infants, the elderly). Many patients with *Salmonella* gastroenteritis benefit from symptomatic therapy with opiates. Restoration of fluid and electrolyte balance is essential if dehydration is present. If specific therapy is needed, chloramphenicol [Chloromycetin] and ampicillin are the agents of choice; the antibiotic should be given for 10 to 14 days.

Orally administered antibiotics are used in the treatment of enteropathogenic *Escherichia coli* infections: neomycin [Mycifradin, Neobiotic] or kanamycin [Kantrex] are drugs of first choice; ampicillin, tetracyclines,

furazolidone, polymyxin B [Aerosporin], and paromomycin [Humatin] also are effective.

Ampicillin is the antibiotic of choice in *Shigella* infections. The sulfonamides are effective in bacillary dysentery caused by sensitive strains of *Shigella*, but they are no longer considered as primary therapy because of the prevalence of resistant strains. For sensitive strains, sulfadiazine, sulfisoxazole [Gantrisin], or ampicillin is given for seven to ten days. Alternative drugs for oral use in patients with infections caused by resistant strains of *Shigella* or when clinical failure occurs are kanamycin, tetracyclines, furazolidone, polymyxin B, and paromomycin. Genetic transfer of resistance to one or more antibiotics occurs between *Shigella* and other enteric gram-negative bacteria, so antimicrobial agents must be judiciously selected and used.

Salicylazosulfapyridine [Azulfidine] is used as adjunctive therapy in patients with ulcerative colitis.

Treatment with polymyxin B or gentamicin [Garamycin] plus carbenicillin [Geopen, Pyopen] is useful in acute enteritis due to *Pseudomonas* infection.

Antibiotics effective in the treatment of acute gastroenteritis due to *Proteus* infection include tetracyclines, gentamicin, kanamycin, neomycin, and clindamycin [Cleocin].

See also Chapters 48, Penicillins; 52, Polymyxins; 53, Tetracyclines; 54, Chloramphenicol and Derivatives; 55, Sulfonamides; and 57, Aminoglycoside Antibacterial Agents and Miscellaneous Antimicrobial Drugs.

Cholestyramine resin is useful in the treatment of watery diarrhea caused by changes in the distribution of bile acids; this occurs in patients with distal ileal resections of less than 100 cm and in those with colonization of the upper small intestine by colonic flora.

Adverse Reactions and Precautions

Opiate preparations should not be used for prolonged, unsupervised periods because of their potential for abuse, although this is minimal in doses used for diarrhea. They should not be used in diarrhea caused by poisoning until the toxic material has been eliminated from the gastrointestinal tract. Untoward effects from the usual antidiarrheal doses are uncommon, but larger doses may produce the undesirable effects of the opiates (see Chapter 21, Strong Analgesics). The dependence liability of diphenoxylate hydrochloride with atropine [Lomotil] is slight, and reactions occur infrequently with usual doses (see the evaluation on Diphenoxylate Hydrochloride with Atropine). The opiates must be used with caution in patients acutely ill with ulcerative colitis or ischemic colonic disease, since they can precipitate adynamic ileus of the colon and possibly toxic dilatation. They also should be used cautiously in patients with hepatic dysfunction.

Anticholinergics (eg, propantheline [Pro-Banthine]), when used in therapeutic doses, have caused dryness of the mouth, visual disturbances, dizziness, headache, increased intraocular pressure, dysuria, tachycardia, drowsiness, and rash. Like the opiates, the anticholinergics may facilitate dilatation in acute ulcerative or ischemic disease of the colon. (See Chapter 78, Antispasmodics.)

The adsorbents are usually safe, but their continued use has produced impaction in very young, old, or debilitated patients; they also may interfere with absorption of bile salts and drugs.

The preparations containing poorly absorbed antibiotics are hazardous in patients with extensive intestinal lesions, which might lead to significant absorption. Enough neomycin has been absorbed from the gastrointestinal tract to produce deafness (see the evaluation on Neomycin Sulfate in Chapter 57, Aminoglycoside Antibacterial Agents and Miscellaneous Antimicrobial Drugs). This danger is particularly great in patients with impaired renal function.

Intestinal candidiasis and the dangerous complication of acute pseudomembranous enterocolitis have been observed after therapy with many orally administered antibiotics. The use of vancomycin [Vancocin] should be considered if the latter condition develops.

Fatal secondary staphylococcal intestinal infection has been reported after the prophylactic use of neomycin in adults.

When poorly absorbed antibacterial agents are given for a long period, the physician should be alert for the possible development of hypoprothrombinemia due to reduced vitamin K synthesis by intestinal bacteria.

Many mixtures containing poorly absorbed antibacterial agents with adsorbents and protectants frequently provide suboptimal antibacterial dosages and yet subject the patient to the potential adverse effects of these agents.

AMA DRUG EVALUATIONS

Cholestyramine resin [Cuemid, Questran] may cause steatorrhea or constipation.

INDIVIDUAL EVALUATIONS

BISMUTH SUBCARBONATE

Bismuth salts (most commonly bismuth subcarbonate) are used as supposed protectants and adsorbents in the treatment of diarrhea. There is no evidence, other than tradition, that they have any beneficial effect in diarrhea or contribute to the action of any mixtures containing them.

USUAL DOSAGE.—The usual suggested dosage for bismuth subcarbonate is: *Oral: Adults*, 1 to 4 g, suspended in water, every two to four hours.

PREPARATIONS.—*Oral:* Powder; tablets 300 mg. Drug marketed under generic name.

CHOLESTYRAMINE RESIN [Cuemid, Questran]

Cholestyramine is useful in many patients with diarrhea caused by changes in distribution of the bile acids. These include patients with ileal resections of less than 100 cm, whose diarrhea is caused by an increase in concentration of bile acids in solution in the colon, and those with colonization of the upper small intestine by colonic flora. In patients with extensive ileal resections who are eating a normal diet, cholestyramine generally does not lessen diarrhea and it increases steatorrhea. In these patients, the concomitant use of cholestyramine and a low-fat diet supplemented with medium-chain triglycerides may control diarrhea while permitting caloric balance.

For other uses, see Chapter 13, Agents Used to Treat Hyperlipidemia.

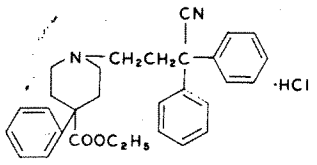
USUAL DOSAGE.—*Oral: Adults*, 4 g four times daily before meals; the preparation is suspended in 180 to 240 ml of water or, when necessary, a fluid. The drug should never be swallowed dry because of the hazard of esophageal irritation or blockage.

PREPARATIONS.—

Cuemid (Merck Sharp & Dohme). *Oral:* Powder in 216 g containers.

Questran (Mead Johnson). *Oral:* Powder in 4 g packets.

DIPHENOXYLATE HYDROCHLORIDE WITH ATROPINE [Lomotil]



The effectiveness of diphenoxylate hydrochloride is comparable to that of the opium extracts. It apparently acts by increasing intestinal tone and inhibiting intestinal propulsive motility.

Diphenoxylate hydrochloride with atropine has minimal potential for producing physical dependence when administered in the recommended dosage range, and is classified as a Schedule V substance. The incidence of adverse reactions is relatively low. Untoward effects include rash, drowsiness, dizziness, depression, restlessness, abdominal distention, intestinal obstruction, toxic dilatation of the colon, nausea, headache, and blurred vision. Investigationally, large doses (40 to 60 mg) of diphenoxylate produced a morphine-like euphoria, and toxic doses may cause respiratory depression and coma. Narcotic antagonists are effective antidotes. (See Chapter 23, Narcotic Antagonists.) Diphenoxylate may potentiate the actions of barbiturates, opiates, and other depressants. It should be used cautiously in patients with liver disease, since hepatic coma has been precipitated in a patient with cirrhosis.

USUAL DOSAGE.—*Oral: Adults*, 5 mg three or four times daily. *Children 8 to 12 years of age*, 10 mg daily in divided doses; *5 to 8 years*, 8 mg daily in divided doses.

PREPARATIONS.—Lomotil (Searle). *Oral:* Each tablet or 5 ml of liquid contains diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg.

FURAZOLIDONE [Furoxone]

Furazolidone, an antibacterial and antiprotozoal agent, is moderately active against some gram-positive and gram-negative enteric organisms, including species of *Salmonella, Shigella, Escherichia, Proteus, Streptococcus,* and *Staphylococcus.* This drug may be useful in the treatment of severe bacterial enteritis and dysentery caused by susceptible strains of *Salmonella* and *Shigella*, but it will not prevent

the carrier state in these infections and more effective drugs are available. Enteropathogenic *E. coli* infections may respond to furazolidone. This agent also is effective in giardiasis. It is poorly absorbed and does not satisfactorily reduce the bacterial population of the intestine when given preoperatively.

The common adverse effects are nausea and vomiting. Arthralgia, fever, and cutaneous hypersensitivity reactions have been reported. The drug may cause hemolysis in patients deficient in erythrocyte glucose-6-phosphate dehydrogenase. Catabolic products color urine brown. Alcohol should not be used during therapy to avoid a disulfiram-type reaction. The monoamine oxidase inhibiting activity of a metabolite of furazolidone enhances the action of sympathomimetic amines. The safety of this drug during pregnancy and in infants less than 1 month of age has not been determined.

See also the Introductory Statement and Chapter 56, Nitrofurans.

USUAL DOSAGE.—*Oral: Adults,* 100 mg four times daily. *Children 5 years of age or older,* 25 to 50 mg four times daily; *1 to 5 years,* 17 to 25 mg four times daily; *infants 1 month to 1 year,* 8 to 17 mg four times daily.

PREPARATIONS.—Furoxone (Eaton). *Oral:* Tablets 100 mg.

LACTOBACILLUS CULTURES

[Bacid, Lactinex]

Bacid is a culture of *Lactobacillus acidophilus,* and Lactinex is a mixed culture of *L. acidophilus* and *L. bulgaricus (L. bulgaricus* does not colonize in the colon). These viable cultures are promoted as an aid in the restoration of normal intestinal flora after administration of antibacterial drugs; many of these drugs suppress intestinal saprophytes such as lactobacilli and *Bacteroides* and potential pathogens such as staphylococci and *Candida* may then emerge. However, no well-controlled studies supporting use of these preparations have been published.

USUAL DOSAGE.—The manufacturers' suggested dosages are:

Bacid: *Oral:* Two capsules two to four times daily.

Lactinex: *Oral:* Four tablets or 1 g packet three or four times daily.

PREPARATIONS.—

Bacid (USV). *Oral:* Capsules containing *Lactobacillus acidophilus* with carboxymethylcellulose sodium 100 mg.

Lactinex (Hynson, Westcott & Dunning). *Oral:* Granules 1 g packet; tablets 250 mg.

METRONIDAZOLE [Flagyl]

Metronidazole, a trichomonacidal and amebicidal agent, appears to be more effective than furazolidone and equally as effective as quinacrine in the treatment of giardiasis.

The incidence of untoward effects is lowest with metronidazole. The drug occasionally causes nausea and, less commonly, diarrhea. Some patients receiving metronidazole experience a disulfiram-type reaction after the ingestion of alcohol.

For other uses and adverse effects of metronidazole, see Chapter 62, Amebicides and Chapter 64, Antitrichomonal Agents.

USUAL DOSAGE.—*Oral:* For treatment of giardiasis, *adults and children over 30 kg,* 250 mg three times daily; *children 19 to 29 kg,* 250 mg twice daily; *14 to 19 kg,* 125 mg three times daily; *under 14 kg,* 125 mg twice daily. Treatment should be continued for seven days.

PREPARATIONS.—Flagyl (Searle). *Oral:* Tablets 250 mg.

OPIUM TINCTURE

Opium tincture is a traditional preparation that is useful for the symptomatic treatment of diarrhea. It is less widely used today than paregoric because the latter is more dilute and teaspoonful doses are more convenient to measure than the smaller amounts of opium tincture prescribed. An effective antidiarrheal dose is not likely to produce euphoria or analgesia because of the relatively small amount needed to produce an effect on the gastrointestinal tract.

Adverse reactions with usual doses are uncommon, but larger doses may produce the undesirable effects of opiates (see Chapter 21, Strong Analgesics). Opium tincture is classified as a Schedule II drug.

USUAL DOSAGE.—*Oral:* 0.6 ml (range, 0.3 to 1 ml) four times daily. The maximal single dose is 1 ml taken at intervals of 2 to 4 hours, and not more than 6 ml should be taken in 24 hours.

PREPARATIONS.—*Oral:* Tincture 10% containing 10 mg of morphine per milliliter. Drug marketed under generic name.

MIXTURES

DONNAGEL
DONNAGEL PG

Donnagel is a mixture containing kaolin, pectin, and three anticholinergic drugs (atropine, scopolamine, and hyoscyamine). It is of doubtful efficacy (see the Introductory Statement and the evaluation on Kaolin Mixture with Pectin). Donnagel PG combines the effects of the basic formula and opium (see the evaluation on Opium Tincture). This mixture is classified as a Schedule V substance.

The adverse effects are those produced by the individual drugs in the mixtures. (See the appropriate evaluations.) Contraindications of the basic mixture include glaucoma and intestinal obstruction. Donnagel should be administered with care to patients with urinary tract obstruction or prostatic hypertrophy.

USUAL DOSAGE.—No useful dosage is recognized. The manufacturer's suggested dosages are:

Donnagel: *Oral: Adults,* 30 ml initially, then 15 to 30 ml after each evacuation. *Children,* 10 ml initially, then 5 to 10 ml after each evacuation.

Donnagel PG: *Oral: Adults,* 30 ml every three hours or as needed. *Children over 1 year of age,* 10 ml every three hours as needed.

PREPARATIONS.—

Donnagel (Robins). *Oral:* Each 30 ml of suspension contains kaolin 6 g, pectin 142.8 mg, hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, and scopolamine hydrobromide 0.0065 mg.

Donnagel PG (Robins). *Oral:* Each 30 ml of suspension contains the same formulation as Donnagel plus powdered opium 24 mg.

FUROXONE LIQUID

Furoxone Liquid is a mixture of the antibacterial and antiprotozoal agent, furazolidone, with pectin and kaolin. The rationale for this mixture is questionable because furazolidone is effective only in giardiasis and specific enteric bacterial infections caused by sensitive strains, and the effectiveness of kaolin and pectin is doubtful (see the Introductory Statement and evaluation on Kaolin Mixture with Pectin). However, if the tablet form of furazolidone is difficult to administer, this preparation may be considered a liquid dosage form of the drug.

USUAL DOSAGE.—This mixture is useful only as a liquid dosage form of furazolidone. (For recommended dosage of the antimicrobial agent, see the evaluation on Furazolidone.)

PREPARATIONS.—Furoxone Liquid (Eaton). *Oral:* Each 15 ml of liquid contains furazolidone 50 mg, kaolin 3 g, and pectin 225 mg.

KAOLIN MIXTURE WITH PECTIN

Kaolin and pectin each have adsorbent and allegedly protective properties and are promoted for use in the symptomatic treatment of diarrhea. They are customarily available only in preparations that contain both agents and often additional antibacterial drugs as well. Adequately controlled clinical studies that demonstrate the efficacy of kaolin-pectin combinations are lacking, and although their use is supported by tradition, they are of doubtful value. It has been suggested, without verification, that kaolin and pectin adsorb viruses and bacterial toxins.

Kaolin and pectin are contraindicated in patients with obstruction of the bowel. These mixtures should not be used for more than two days, or in patients with fever, or in children less than 3 years of age.

USUAL DOSAGE.—Because proof of efficacy is lacking, no useful dosage is recognized. The suggested N.F. dosage is: *Oral: Adults,* 30 ml repeated as necessary.

PREPARATIONS.—Kaolin Mixture with Pectin, N.F. *Oral:* Suspension containing 20% kaolin and 1% pectin in sweetened, peppermint-flavored tragacanth. Marketed under generic name.

KAOPECTATE

The formula of this mixture is a modification of the formula for Kaolin Mixture with Pectin, N.F. Like the latter, it is of doubtful value. It should not be used for more than two days, or in patients with fever, or in children less than 3 years of age. It is contraindicated in patients with obstruction of the bowel.

USUAL DOSAGE.—Because proof of efficacy is lacking, no useful dosage is recognized. The manufacturers' suggested dose (to be taken after each evacuation) is: *Oral: Adults,* 60 to 120 ml. *Children over 12 years of age,* 60 ml; *6 to 12 years,* 30 to 60 ml; *3 to 6 years,* 15 to 30 ml.

PREPARATIONS.—Kaopectate (Upjohn). *Oral:* Each 5 ml of liquid contains kaolin 1 g and pectin 20 mg.

SIMILAR MIXTURES.—Kalpec (Wyeth),

Kao-Con (Upjohn), Paocin (Beecham-Massengill), Pargel (Parke, Davis).

PAREGORIC

Paregoric (camphorated opium tincture) is an antidiarrheal mixture that contains 0.04% morphine and provides the convenience of teaspoonful doses. It is as effective as opium tincture in the appropriate dose. Paregoric frequently is combined with other antidiarrheal agents.

Adverse effects are rare, but nausea and other gastrointestinal disturbances occur occasionally; the usual oral doses do not produce euphoria or analgesia, but prolonged use has produced dependence despite the unappealing taste of paregoric. Paregoric is classified as a Schedule III drug. It should not be used in diarrhea caused by poisoning until toxic material is eliminated from the gastrointestinal tract.

USUAL DOSAGE.—*Oral: Adults,* 5 to 10 ml every two hours (but not more than four times daily) or until diarrhea is controlled. *Children,* 0.25 to 0.5 ml/kg of body weight after each loose stool. Customary amount per prescription should be 1 or 2 ounces.

PREPARATIONS.—Paregoric, U.S.P. contains 0.4 mg of morphine per milliliter. Drug marketed under generic name and under the name Camphorated Tincture of Opium.

PAREPECTOLIN

This antidiarrheal mixture contains pectin, kaolin, and opium; its effectiveness is primarily due to the opium content, and thus use of the alkaloid alone is preferred. It is classified as a Schedule V substance.

This mixture has the same adverse effects and contraindications as do opium and kaolin mixture with pectin. (See the Introductory Statement and the evaluations on Opium Tincture and Kaolin Mixture with Pectin.)

USUAL DOSAGE.—No useful dosage is recognized because there is no evidence that pectin and kaolin contribute to the antidiarrheal effect. The manufacturer's suggested dosage is: *Oral: Adults,* 15 to 30 ml after each evacuation for no more than four doses in 12 hours. *Children,* 5 to 10 ml after each evacuation for no more than four doses in 12 hours.

PREPARATIONS.—Parepectolin (Rorer). *Oral:* Each 30 ml of suspension contains opium 15 mg, pectin 162 mg, and kaolin 5.5 g.

SIMILAR MIXTURE.—Pecto-Kalin (Lemmon).

SORBOQUEL

Sorboquel is a mixture of polycarbophil and the anticholinergic-antispasmodic, thihexinol methylbromide. Polycarbophil is a hydrophilic polyacrylic resin that may be useful in both constipation and diarrhea because of its marked capacity for binding water. Evidence in support of an enhanced antidiarrheal effect of polycarbophil by the addition of thihexinol is from uncontrolled clinical studies and is unconvincing.

Overdosage with Sorboquel may cause symptoms of atropine poisoning (see Chapter 78, Antispasmodics). The drug is contraindicated in patients with urinary retention, angle-closure glaucoma, and in those in whom tachycardia would be dangerous.

USUAL DOSAGE.—Use of this mixture is not justified because of the potential adverse effects of thihexinol and inadequate evidence that it contributes to the antidiarrheal effect of polycarbophil. The manufacturer's suggested dosage is: *Oral: Adults and children over 12 years of age,* one tablet four times daily; six to eight tablets daily may be given in severe cases. The dose should be reduced after diarrhea has responded to treatment.

PREPARATIONS.—Sorboquel (Schering). *Oral:* Each tablet contains polycarbophil 500 mg and thihexinol methylbromide 15 mg.

Additional Antidiarrheal Mixtures

The following antidiarrheal mixtures are listed for information only.

Cerebel (Xttrium): Each 5 ml of liquid contains cerium oxalate 300 mg, hyoscyamine sulfate 5.2 μg, scopolamine hydrobromide 3 μg, atropine sulfate 0.01 mg, milk of bismuth 2.5 ml, and phenobarbital elixir 2.02 ml; each capsule contains cerium oxalate 300 mg, bismuth subcarbonate 300 mg, and powdered extract of belladonna alkaloids 8 mg.

Corrective Mixture (Beecham-Massengill): Each 5 ml of elixir contains zinc phenolsulfonate 10 mg, phenyl salicylate 20 mg, bismuth subsalicylate 80 mg, and pepsin 40 mg with or without paregoric 0.6 ml.

Infantol (First Texas): Each 30 ml of suspension contains pectin 260 mg, zinc phenolsulfonate 104 mg, bismuth subsalicylate 518 mg, and chondrus extract with (Pink) or without (White) paregoric 3.6 mg.

Kaomagma (Wyeth): Each 5 ml of suspension contains kaolin 1 g in aluminum hydroxide gel.

Metropectin (Pennwalt): Each tablet contains

methylatropine nitrate 1 mg, kaolin 450 mg, pectin 60 mg, aluminum hydroxide 120 mg, and beta lactose 60 mg.

Mul-Sed (Webster): Each 5 ml of liquid contains paregoric 1.25 ml, pectin 43.2 mg, kaolin 860 mg, and milk of bismuth 0.8 ml.

Parelixir (Purdue Frederick): Each 5 ml of liquid contains tincture of opium 0.03 ml and pectin 24 mg.

Pectocel (Lilly): Each 5 ml of suspension contains pectin 50 mg, kaolin 1 g, and zinc phenolsulfonate 12 mg.

Pektamalt (Warren-Teed): Each 5 ml contains pectin 109 mg and kaolin 1.09 g with potassium gluconate and sodium citrate.

Chapter 81

LAXATIVES AND AGENTS AFFECTING FECAL CONSISTENCY

Laxatives and drugs that affect fecal consistency facilitate the passage of feces through the colon and their elimination from the rectum. The proper uses of these drugs are to ease defecation in those with painful hemorrhoids or other rectal disorders; to avoid excessive straining and concurrent increases in abdominal pressure in those with hernias; to avoid potentially hazardous increases in blood pressure during defecation in patients with hypertensive, cerebral, coronary, or other arterial diseases; to relieve acute constipation; to cleanse the bowels prior to radiologic and proctologic examinations and bowel surgery; to remove parasites and toxic vermifuge after anthelmintic therapy; and to remove the toxic material in some cases of poisoning.

In the past, drugs of this type were classified according to the vigor of their action as laxatives (mildest), cathartics, and drastics (most irritant). The drastics include the resinous drugs, colocynth, gamboge, elaterin, ipomea, jalap, and podophyllum. The violence of their action often produces hemorrhagic enteritis, and thus use of the drastics is not justified. Croton oil, which is similarly violent in action and has been virtually abandoned because of it, also should not be used. Calomel (mercurous chloride), once widely used as a cathartic, should not be used because it is unsafe and unreliable. A more useful classification, based on mechanism of action, is: stimulants, bulk-forming agents, saline cathartics, lubricants, and wetting agents.

Stimulants: The exact mechanism of action of each drug in this group has not been established. In general, however, they produce defecation by stimulating peristalsis either by acting on the intestinal intramural nerve plexus, smooth muscle, electrolyte transport system, or some combination of these.

Castor oil has been classified as a stimulant cathartic because lipolytic action in the small intestine liberates ricinoleic acid, which stimulates the motor activity of the small intestine by an unknown mechanism to produce defecation.

The anthraquinone-containing group of stimulant cathartics (eg, casanthranol, cascara, senna, danthron [Danivac, Dorbane], rhubarb, aloe) is widely used. These drugs act principally on the large intestine which they reach both directly after passage through the small intestine and indirectly by way of the bloodstream, since some is absorbed. Of these, cascara has the mildest action and will produce a soft or formed stool with little or no colic. Danthron, a synthetic anthraquinone, also has a mild effect. Crude senna is somewhat more active. Rhubarb and aloe are the most potent; since they are most likely to cause colic, they should not be used. Casanthranol, a glycoside-containing extract of cascara, is reported to be ten times more potent than cascara.

Phenolphthalein is presumably a stimulant cathartic. It acts primarily on the large intestine and produces a semifluid or soft stool with little or no colic.

Oxyphenisatin is similar pharmacologically to phenolphthalein and is administered rectally to produce defecation. The acetate ester of this compound has been withdrawn from the market because its prolonged oral use caused hepatitis and jaundice.

Bisacodyl [Dulcolax], which also is similar pharmacologically to phenolphthalein, stimulates the sensory nerve endings of the colonic mucosa to initiate reflex peristalsis which, in turn, produces defecation.

Glycerin suppositories promote defecation by stimulating the rectal mucosa; they also may soften inspissated fecal material.

Bulk-Forming Agents: The bulk-producing laxatives (bran, gum tragacanth, chondrus, sterculia [karaya] gum, bassora gum, carboxymethylcellulose, agar, plantago seed, and psyllium hydrophilic colloid) absorb water and expand. This expanded indigestible and unabsorbable material increases the bulk of the intestinal contents, thereby producing a reflex peristalsis and defecation. The absorbed water also softens the stool. Bulk laxatives are most effective if taken with one or more glasses of water. The most commonly used preparations are those containing psyllium hydrophilic colloid which is derived from plantago seeds. Allergic reactions (urticaria, nonseasonal rhinitis, dermatitis, and bronchial asthma) are a serious drawback to the use of the plant gums.

Saline Cathartics: These agents include a group of salts, one or both ions of which are poorly absorbed. A hypertonic solution of such a salt osmotically draws a substantial amount of fluid into the intestine, and the presence of this fluid causes increased peristalsis and defecation. The commonly used salts in this class are magnesium carbonate, oxide, citrate, hydroxide, or sulfate; sodium sulfate or phosphate; and mixed sodium and potassium tartrate. The saline cathartics also are used after the ingestion of anthelmintics or poisons to hasten the evacuation of the worms or toxic materials.

Lubricants: Mineral oil (liquid petrolatum), olive oil, and cottonseed oil usually are considered to be the representatives of this group. However, the digestible oils have now fallen into disuse and only mineral oil is currently used. When administered orally, mineral oil softens the feces and is used when it is important to lessen the strain of evacuation (eg, in patients with hernia or cardiovascular disease). When administered rectally, it eases the passage of impacted fecal material. Its mechanism of action is not known.

Wetting Agents: Dioctyl sodium sulfosuccinate [Colace, Doxinate], dioctyl calcium sulfosuccinate [Surfak], and poloxalkol [Magcyl, Polykol] soften the feces by lowering their surface tension; this permits the fecal mass to be penetrated by intestinal fluids. They are used when it is important to lessen the strain of evacuation.

Adverse Reactions and Precautions

Laxatives should be used only for short-term therapy. Most physicians probably have more patients who should break the habit of taking laxatives than they have patients who need such drugs. The addition to the diet of such natural laxatives as high residue foods, figs, or prunes, and the establishment of a regular time for defecation (eg, after breakfast) may help those in the first group.

A laxative should never be given to a patient with undiagnosed abdominal pain, intestinal obstruction, or fecal impaction. A change in bowel habit that persists must be thoroughly investigated.

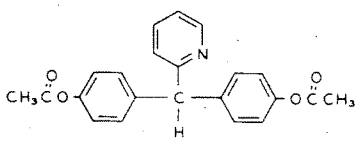
The prolonged continuous use of the stimulant drugs may result in spastic colitis, sodium depletion, hypokalemia, dehydration, secondary aldosteronism, steatorrhea, protein-losing gastroenteropathy with hypoalbuminemia, changes in intestinal anatomy, and osteomalacia.

Because it is possible that obstruction or impaction may occur after use of the bulk-forming agents, these drugs should not be used by those with dysphagia or intestinal ulcerations, adhesions, or stenosis.

See also the individual evaluations.

STIMULANTS

BISACODYL [Dulcolax]



Bisacodyl is a mild stimulant laxative that is active orally and rectally. It produces a copious soft to formed stool within six hours after oral administration and within one hour after rectal administration.

The tablets should be swallowed whole to avoid gastric irritation; they should not be taken within one hour after ingestion of milk or antacids in order to prevent dissolution of the enteric coating, release of the drug, and resultant gastric irritation. Mild colic has been reported. The suppository may produce mild smarting or tenesmus, and continued administration can cause mild rectal irritation. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.--

Oral: Adults, 10 to 15 mg; *children*, 5 to 10 mg.

Rectal: Adults and children over 2 years of age, 10 mg; *under 2 years*, 5 mg.

PREPARATIONS.—Dulcolax (Geigy).
Oral: Tablets (enteric-coated) 5 mg.
Rectal: Suppositories 10 mg.

CASANTHRANOL [Peristim Forte]

Casanthranol is a purified mixture of the anthranol glycosides extracted from cascara sagrada. It is a member of the anthraquinone-containing group of stimulant laxatives (see the Introductory Statement), and is reported to be ten times as potent as whole cascara sagrada. In most patients, a semisoft stool is produced by casanthranol in 8 to 12 hours.

Adverse reactions that have been reported are abdominal cramping, diarrhea, and nausea and rectal bleeding in a patient with ulcerative colitis. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults,* 90 mg at bedtime; in stubborn cases, 180 mg may be required.

PREPARATIONS.—Peristim Forte (Mead Johnson). *Oral:* Capsules 90 mg.

CASTOR OIL
CASTOR OIL, AROMATIC
CASTOR OIL, EMULSIFIED [Neoloid]

Castor oil is a stimulant laxative which produces one or more copious, watery evacuations approximately two to six hours after ingestion. Normal evacuation may be delayed one or more days after its use. This drug is more active if taken on an empty stomach. Since it thoroughly empties gas and feces from the intestines, castor oil is used in the preparation of patients for proctoscopy, bowel surgery, or radiologic studies of the gastrointestinal tract. Fruit juice or carbonated drinks help disguise the disagreeable taste. Neoloid is a mint-flavored emulsion of castor oil.

No adverse reactions have been reported. For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—

Castor Oil; Castor Oil, Aromatic:

Oral: Adults, 15 to 30 ml; *children,* 5 to 15 ml.

Castor Oil, Emulsified:

Oral: Adults, 30 to 60 ml; infants, 2.5 to 7.5 ml; *children,* dose adjusted between that used for infants and adults.

PREPARATIONS.—

Castor Oil, U.S.P., Castor Oil, Aromatic, N.F. Marketed under generic name.

Castor Oil, Emulsified: Neoloid (Lederle). *Oral:* Liquid 36.4%.

CASCARA SAGRADA

Cascara is the mildest member of the anthraquinone group of stimulant laxatives. Its effect on the small intestine is slight, but it causes vigorous peristalsis in the large intestine. The drug produces a soft or formed stool in six to eight hours with little or no colic.

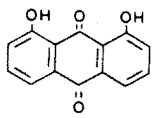
The prolonged use of cascara preparations produces benign pigmentation of the colonic mucosa (melanosis coli) that may regress after the drug is discontinued. Since the active principles of cascara are excreted in milk, this laxative should not be given to lactating mothers. The drug imparts a yellowish-brown color to acid urine and a reddish color to alkaline urine. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults,* 300 mg of extract, 1 ml of fluidextract, or 5 ml of aromatic fluidextract.

PREPARATIONS.—Cascara Tablets, N.F., Cascara Sagrada, U.S.P., Cascara Sagrada Extract, N.F., Cascara Sagrada Fluidextract, N.F., Aromatic Cascara Fluidextract, U.S.P.

AVAILABLE TRADEMARK.—Cas-Evac (Parke, Davis). Forms also marketed under generic name.

DANTHRON [Danivac, Dorbane]



This synthetic anthraquinone derivative has the same mode of action as other stimulant laxatives (see the Introductory Statement). It produces a soft or semifluid stool in six to eight hours. Danthron is much less active than an equivalent dose of the glycosides in the anthraquinone-containing stimulant laxatives.

Brownish discoloration of the rectal mucosa has been reported after prolonged use of danthron. This disappears after the drug is discontinued. Danthron is excreted in milk and should not be given to lacating mothers. It also is excreted in urine and imparts a pink color to alkaline urine. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults,* 75 to 150 mg.

PREPARATIONS.—Danivac (Fellows-Testagar), Dorbane (Riker). *Oral:* Tablets 75 mg. Drug also marketed under generic name.

GLYCERIN SUPPOSITORIES

Glycerin suppositories contain by weight approximately 91% glycerin, 9% sodium stearate, and 5% water. They promote fecal evacuation in 15 to 30 minutes by stimulating the rectal mucosa. They also may soften inspissated fecal material.

Glycerin suppositories should not be used in the presence of anal fissures, fistulas, ulcerative hemorrhoids, or proctitis. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Rectal: Adults and children*, one suppository.

PREPARATIONS.—Glycerin Suppositories, N.F. Drug marketed under generic name.

OXYPHENISATIN [Lavema Enema Powder]

This drug is a potent stimulant laxative. It is administered rectally, and acts upon the colon to produce defecation within a few minutes. Its efficacy relative to other substances used as enemas (eg, isotonic sodium chloride solution) is, however, as yet unknown.

The acetate ester of this drug was widely used as an orally administered laxative. However, it has been withdrawn from the market because of its toxicity. (See also the Introductory Statement.)

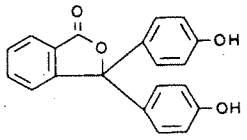
Cramps, diarrhea, nausea, vomiting, sweating, tachycardia, and syncope occur infrequently after the use of this drug.

USUAL DOSAGE.—*Rectal: Adults*, prior to diagnostic or surgical procedures, one-half to one packet dissolved in 1 to 2 liters of water; *elderly or debilitated patients*, one-half packet in 1 liter of water. For severe constipation, one-half to one packet dissolved in 180 ml of water. As a barium enema adjuvant, one-half to one packet mixed with 1 or 2 liters of barium enema suspension; *elderly or debilitated patients*, one-half packet.

PREPARATIONS.—Lavema Enema Powder (Winthrop). *Rectal:* Each packet contains oxyphenisatin 20 mg with disodium edetate, sodium stearate, and lactose in sufficient quantity to make 3 g.

AVAILABLE MIXTURE.—Lavema Compound Solution Disposable Enema Kit (Winthrop): Each 180 ml contains oxyphenisatin 20 mg, tyloxapol 135 mg, and propylene glycol 9 ml.

PHENOLPHTHALEIN



Phenolphthalein is a stimulant laxative which acts primarily on the large intestine to produce a semifluid stool in four to eight hours with little or no colic. Its action may persist for three to four days as a result of the enterohepatic circulation of the small amounts absorbed. Phenolphthalein is the active agent in many proprietary over-the-counter laxative preparations.

Dermatitis, particularly fixed drug eruptions, with pruritus, burning, vesication, and discoloration may occur in hypersensitive patients. Fatal hypersensitivity reactions also have been reported but a causal relationship to phenolphthalein has not been established. Occasional cases of nonthrombocytopenic purpura have occurred. Phenolphthalein imparts a red color to alkaline urine or alkaline feces. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults*, 60 mg, but as much as 200 mg has been given.

PREPARATIONS.—Phenolphthalein, N.F.; Phenolphthalein Tablets, N.F.

AVAILABLE TRADEMARK.—Phenolax (Upjohn). Drug also marketed in bulk form under generic name.

SENNA PREPARATIONS

Senna is an anthraquinone-type stimulant laxative with actions similar to those of cascara, but it is more active and produces more colic. Defecation occurs within six hours.

Senna is available as the crude drug, as the crystalline senna glycosides (sennosides A and B), and as a standardized senna concentrate [Senokot] which is purified and standardized. The purified preparations are more commonly used than the crude ones and are claimed to produce colic and loose stools only rarely; however, evidence supporting this claim is limited.

The drug imparts a yellowish-brown color to acid urine and a reddish color to alkaline urine. See also the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—

Senna:

Oral: Senna, N.F.: *Adults*, 2 g; *children*, 4 mg/kg of body weight. Senna Fluidextract, N.F.: *Adults*, 2 ml; *children*, 0.04 ml/kg. Senna Syrup, N.F.: *Adults*, 8 ml; *children*, 0.15 ml/kg.

Senokot:

Oral: (Granules) *Adults*, 1 level teaspoonful to a maximum of 2 level teaspoonsful two times daily; *geriatric, obstetric, or gynecologic patients and children over 27 kg*, dosage reduced by one-half. (Syrup) *Adults*, 2 to 3 teaspoonsful one or two times daily; *geriatric, obstetric, or gynecologic patients*, dosage reduced by one-half; *children 5 to 15 years of age*, 1 to a maximum of 2 teaspoonsful two times daily; *1 to 5 years*, one-half to a maximum of 1 teaspoonful two times daily; *1 month to 1 year*, one-quarter to a maximum of one-half teaspoonful twice daily. (Tablets) *Adults*, two tablets to a maximum of four tablets two times daily; *geriatric, obstetric, or gynecologic patients and children over 27 kg*, dosage reduced by one-half.

Rectal: Adults, one suppository; *children over 27 kg*, one-half suppository.

Glysennid:

Oral: Adults, one or two tablets before retiring; *children over 10 years of age*, one or two tablets; *6 to 10 years*, one tablet.

PREPARATIONS.—

Senna, N.F., Senna Fluidextract, N.F., Senna Syrup, N.F.

Senokot (Purdue Frederick).

Oral: Granules, syrup, tablets.

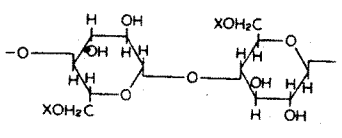
Rectal: Suppositories.

Glysennid (Sandoz). *Oral:* Tablets.

AVAILABLE TRADEMARKS.—Senna: Aperens (Brayten), Casafru (Davies Rose Hoyt), Roenten (Mallinckrodt). Forms also marketed under generic name.

BULK-FORMING AGENTS

CARBOXYMETHYLCELLULOSE SODIUM
[Bu-Lax, C.M.C.]



X = H or CH_2CO_2Na

This bulk-forming laxative is a synthetic hydrophilic colloid which is indigestible and nonabsorbable and does not interfere with the intestinal absorption of essential nutrients. It usually produces its laxative effect within 12 to 24 hours but up to three days of medication may be necessary to achieve a full effect. Carboxymethylcellulose is claimed to aid in the treatment of obesity and acute diarrhea, but the evidence supporting these claims is not convincing.

For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults*, 1.5 g two to four times daily; *children*, 500 mg two or three times daily. The drug should be taken with one or two glasses of water and ingested rapidly.

PREPARATIONS.—Bu-lax (Ulmer), C.M.C. (Robinson). *Oral:* Tablets 500 mg. Drug also marketed in bulk form under generic name.

PLANTAGO SEED (Psyllium Seed)

This bulk-forming laxative consists of the whole or powdered seeds of one of three species of *Plantago*. It usually produces its laxative effect within 12 to 24 hours but up to three days of medication may be necessary to achieve a full effect. It is indigestible, nonabsorbable, and does not interfere with absorption of essential nutrients. Plantago seed is alleged to aid in the treatment of obesity and acute diarrhea, but its efficacy for these purposes has not been proved.

For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults*, 4 to 15 g in a glass of water, one to three times daily. The drug should be ingested rapidly.

PREPARATIONS.—Plantago Seed, N.F. Drug marketed under generic name and under the name Psyllium Seed.

PSYLLIUM HYDROPHILIC COLLOID
[Effersyllium, Metamucil, Mucilose, Plantamucin, Testarr]

This bulk-forming laxative is the refined colloid from psyllium seeds. It usually produces its laxative effect within 12 to 24 hours but up to three days of medication may be necessary to achieve a full effect. The preparation is indigestible, nonabsorbable, and will not interfere with the intestinal absorption of essential nutrients. Psyllium hydrophilic colloid is alleged to aid in the treatment of obesity and acute diarrhea, but evidence supporting these claims is not convincing.

For general precautions, see the section on adverse reactions and precautions in the

Introductory Statement.

USUAL DOSAGE.—*Oral: Adults,* 1 rounded teaspoonful (7 g) or one packet (instant mix) is mixed with a glass of water or other suitable fluid; the liquid is ingested rapidly one to three times daily. A second glass of water improves the effect.

PREPARATIONS.—

Effersyllium (Stuart). *Oral:* Granular powder.

Metamucil (Searle). *Oral:* Powder in effervescent (instant mix) and noneffervescent form.

Mucilose (Winthrop). *Oral:* Granules, flakes.

Plantamucin (Elder). *Oral:* Granules.

Testarr (Fellows-Testagar). *Oral:* Powder.

SALINE CATHARTICS

MAGNESIUM AND SODIUM SALTS

Many different salts with essentially the same actions are used as saline cathartics. They produce a watery or semifluid evacuation in two to six hours. Saline cathartics are most effective if taken with substantial amounts (at least 240 ml) of fluid on an empty stomach. They are also useful in eliminating the parasites and toxic vermifuge after anthelmintic therapy and in removing the toxic material in some cases of poisoning.

The magnesium and potassium salts are contraindicated in patients with impaired renal function. The bitter taste of magnesium sulfate may cause nausea. The magnesium salts should not be used with neomycin. The sodium salts are contraindicated in cardiac patients with edema or evidence of congestive heart failure, or in those on a low-sodium diet. For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

For dosages, see the following table:

PREPARATIONS	USUAL DOSAGE (Adults)*†
Fleet Enema (Fleet) (solution containing 16 g sodium biphosphate and 6 g sodium phosphate/100 ml)	4 oz (rectal only)
Magnesium carbonate, N.F.	8 g
Magnesium citrate solution, N.F. (1.55 to 1.9 g/100 ml magnesium oxide with citric acid and sodium bicarbonate for effervescence)	200 ml
Milk of Magnesia, U.S.P. (7.5% to 8.5% magnesium hydroxide suspension)	15 ml
Magnesium oxide, U.S.P.	4 g
Magnesium sulfate, U.S.P.	15 g
Phospho-Soda (Fleet) (solution containing 48 g sodium biphosphate and 18 g sodium phosphate/100 ml)	10 to 20 ml
Potassium bitartrate	2 g
Potassium phosphate	4 g
Potassium sodium tartrate, N.F.	10 g
Sodium phosphate, N.F.	4 g
Sodium phosphate, effervescent, dried, N.F.	10 g
Sodium sulfate	15 g
Seidlitz powders (blue powder paper, sodium bicarbonate 2.5 g and potassium sodium tartrate 7.5 g; white powder paper, tartaric acid 2.2 g)	Contents of one blue and white powder paper mixed in about 60 ml of water.
Travad Enema (Flint) (solution containing sodium biphosphate 16 g and sodium phosphate 6 g/100 ml)	4.5 oz (rectal only)

*Dosage is reduced for children (see table, back cover).

†Except where indicated, all doses are to be administered orally. Many manufacturers market their own flavored versions of the various saline cathartics, which tend to be more expensive than the official preparations.

LUBRICANTS

MINERAL OIL (Liquid Petrolatum)

Mineral oil is an indigestible hydrocarbon oil of limited absorbability. It is used orally to lessen the strain of evacuation (eg, in patients with hernia or cardiovascular disease) or rectally to ease the passage of impacted fecal material. The emulsified preparations may reduce seepage through the anal sphincter and may be more effective than the nonemulsified preparation.

Prolonged oral use (more than two weeks) reduces the absorption of the fat-soluble vitamins (A, D, E, and K). The user should be alerted to the risk of lipid pneumonia if mineral oil is aspirated and to the possibility of untoward effects from its absorption. Because of this possibility, its use with the wetting agents, which presumably may increase its absorption, is contraindicated. Mineral oil should not be used after anorectal surgery, for it may cause pruritus ani and interfere with healing of tissue. For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

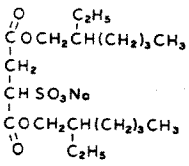
USUAL DOSAGE.—*Oral, Rectal: Adults,* 15 to 45 ml at bedtime.

PREPARATIONS.—Mineral Oil; Mineral Oil Emulsion, N.F.; Mineral Oil, Light, N.F.

AVAILABLE TRADEMARKS.—Fleet Oil Retention Enema (Fleet), Kondremul (Cooper), Petrogalar, Plain (Wyeth). Forms also marketed under generic name.

WETTING AGENTS

DIOCTYL CALCIUM SULFOSUCCINATE [Surfak]
DIOCTYL SODIUM SULFOSUCCINATE [Colace, Doxinate]



These wetting agents soften the feces and are used when it is necessary to lessen the strain of defecation (eg, in persons with hernia or cardiovascular disease). They require one to two days to exert their full effect. These drugs are often combined with other agents, but their use with mineral oil is contraindicated because of the presumption that they may increase the absorption of the oil and thus the possibility of untoward effects.

Diarrhea is the only reported adverse reaction. For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults and children over 12 years of age,* 50 to 240 mg daily; *6 to 12 years,* 40 to 120 mg daily; *3 to 6 years,* 20 to 60 mg daily; *under 3 years,* 10 to 40 mg daily.

PREPARATIONS.—

Dioctyl Calcium Sulfosuccinate:

Surfak (Hoechst). *Oral:* Capsules 50 and 240 mg.

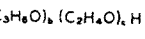
Dioctyl Sodium Sulfosuccinate:

Colace (Mead Johnson). *Oral:* Capsules 50 and 100 mg; solution 10 mg/ml; syrup 20 mg/5 ml.

Doxinate (Hoechst). *Oral:* Capsules 60 and 240 mg; solution 50 mg/ml.

ADDITIONAL TRADEMARKS.—**Dioctyl Sodium Sulfosuccinate:** D-S-S (Parke, Davis), Definate (Fellows-Testagar), Diomedicone (Medicone), Diosuccin (Consolidated Midland), Doss Capsules (Ferndale), Ilozoft (Warren-Teed), Kosate (Lemmon), Laxinate (Mallard), Parlax (Robinson).

POLOXALKOL [Magcyl, Polykol]



The actions and uses of this wetting agent are similar to those of dioctyl calcium sulfosuccinate and dioctyl sodium sulfosuccinate (see the evaluation).

Poloxalkol should not be administered with mineral oil because it is presumed that this drug may increase the absorption of mineral oil and thus the possibility of untoward effects. For general precautions, see the section on adverse reactions and precautions in the Introductory Statement.

USUAL DOSAGE.—*Oral: Adults,* 250 mg two or three times daily; *children 6 to 12 years of age,* 250 to 500 mg daily.

PREPARATIONS.—Magcyl (Elder), Polykol (Upjohn). *Oral:* Capsules 250 mg.

MIXTURES

Sufficient evidence is not available to determine the usefulness of laxative mixtures. The following partial listing of available mixtures is provided only for informational

purposes; inclusion does not imply a recommendation for use.

Agoral (Warner-Chilcott): Each 100 ml of emulsion contains phenolphthalein 1.3 mg in mineral oil.

Alophen (Parke, Davis): Each capsule or pill contains aloin 16 mg, belladonna extract 2.7 mg, ipecac 4.3 mg, and phenolphthalein 32.4 mg.

Bassoran, Plain (Merrell-National): Granules containing sterculia gum 87% and magnesium trisilicate 8.7%.

Bassoran with Cascara (Merrell-National): Each 30 mg of granules contains sterculia gum 75%, magnesium trisilicate 7.5%, and cascara extract 4.4 ml.

Bicholax (Elder): Each tablet contains phenolphthalein 32.4 mg with cascara sagrada extract, sodium glycocholate, sodium taurocholate, and aloin.

Billotabs (Fellows-Testagar): Each tablet contains ox bile extract 30 mg, phenolphthalein 30 mg, cascara sagrada extract 30 mg, aloin 8 mg, and podophyllin 3 mg.

Casakol (Upjohn): Each capsule or 5 ml of syrup contains poloxalkol 250 mg and casanthranol 30 mg.

Casyllium (Upjohn): Each 30 ml of granules contains cascara fluidextract aromatic 13.80 ml, psyllium husk powder 19.44 g, and prune powder 5.53 g.

Clysodrast (Barnes-Hind): Each packet contains bisacodyl 1.5 mg and tannic acid 2.5 g.

Dialose (Stuart): Each capsule contains dioctyl sodium sulfosuccinate 100 mg and carboxymethylcellulose sodium 400 mg.

Dialose Plus (Stuart): Each capsule contains casanthranol 30 mg, dioctyl sodium sulfosuccinate 100 mg, and carboxymethylcellulose sodium 400 mg.

Dorbantyl (Riker): Each capsule contains danthron 25 or 50 mg and dioctyl sodium sulfosuccinate 50 or 100 mg.

Doxan (Hoechst): Each tablet contains danthron 50 mg and dioctyl sodium sulfosuccinate 60 mg.

Doxidan (Hoechst): Each capsule contains danthron 50 mg and dioctyl calcium sulfosuccinate 60 mg.

Gentlax (Purdue Frederick): Each tablet or 5 ml of granules contains guar gum 1 g and standardized senna concentrate 326 mg.

Gentlax S (Purdue Frederick): Tablets containing standardized senna concentrate 187 mg and dioctyl sodium sulfosuccinate 50 mg.

Kondremul with Cascara (Cooper): Each 15 ml of emulsion contains mineral oil 55% and cascara extract 660 mg in chondrus extract.

Kondremul with Phenolphthalein (Cooper): Each 5 ml of emulsion contains mineral oil 55% and phenolphthalein 130 mg in chondrus extract.

Milkinol (Kremers-Urban): Liquid containing dioctyl sodium sulfosuccinate and mineral oil.

Modane (Warren-Teed): Each tablet contains pantothenate calcium 25 mg and danthron 75 mg; each tablet (mild) or 5 ml of liquid contains pantothenate calcium 12.5 mg and danthron 37.5 mg.

Neo-Kondremul (Cooper): Each 5 ml of emulsion contains casanthranol 30 mg in mineral oil and chondrus.

Neolax (Central): Each tablet contains dehydrocholic acid 240 mg and dioctyl sodium sulfosuccinate 50 mg.

Oxiphen (Webster): Each tablet contains sodium glycocholate 16.2 mg, sodium taurocholate 16.2 mg, phenolphthalein 32.4 mg, cascara extract 32.4 mg, and aloin 8.1 mg.

Peri-Colace (Mead Johnson): Each capsule contains casanthranol 30 mg and dioctyl sodium sulfosuccinate 100 mg; each 5 ml of syrup contains casanthranol 10 mg and dioctyl sodium sulfosuccinate 20 mg.

Petrogalar, Cascara (Wyeth): An aqueous suspension of mineral oil with cascara 13.2%.

Petrogalar, Phenolphthalein (Wyeth): An aqueous suspension of mineral oil with phenolphthalein 0.3%.

Rectalad Enema (Wampole): Solution containing glycerin, potassium oleate, potassium stearate, and dioctyl potassium sulfosuccinate.

Senokap DSS (Purdue Frederick): Each capsule contains standardized senna concentrate 225 mg and dioctyl sodium sulfosuccinate 50 mg.

Senokot w/Psyllium (Purdue Frederick): Each 5 ml of granules contains senna concentrate 450 mg and psyllium husks 1 g.

Siblin (Parke, Davis): Each tablet contains a water-absorbent ingredient from psyllium 65% and thiamine hydrochloride 0.5 mg with karaya gum, agar, and pectin.

Sof-2 (Savage): Each 15 ml of suspension contains bentonite 2.1 g and magnesium sulfate 2 g.

Syllamalt (Abbott): Powder containing diastatic malt extract powder 15%, malt soup extract powder 35%, and psyllium hydrophilic hemicellulose 50%.

Vacuetts (Dorsey): Suppositories containing sodium biphosphate anhydrous, sodium acid pyrophosphate, sodium bicarbonate, and polyethylene glycols.

Chapter 82

ANORECTAL PREPARATIONS

Hemorrhoids, anal fissures, and related benign conditions are common and often cause pruritus and pain, which may become excruciating, especially during defecation. Of the many proprietary mixtures that are available, a few afford symptomatic relief but none are curative. Most anorectal preparations are suppositories which combine a local anesthetic, emollients, and sometimes a corticosteroid. Some also contain ingredients of questionable rationality such as bismuth salts, menthol, belladonna, opium, vitamins, weak antiseptics, and Peruvian or Nicaraguan balsam. Convincing data that any one mixture is superior to others in relieving symptoms are lacking, although some are probably safer than others.

The local anesthetics commonly incorporated into these preparations include benzocaine, tetracaine, dibucaine, lidocaine, and pramoxine. The bases of local anesthetics penetrate unbroken skin to afford some degree of relief, whereas the salts are effective on mucosa but not on intact perianal skin. In some preparations, the concentration of the base is too low to be active. Benzocaine, one of the most widely used topical anesthetics, exerts no action unless it is present in concentrations of 5% or more. (See also Chapter 18, Local Anesthetics.)

The combinations described in the individual evaluations that follow are those most commonly prescribed; they are not necessarily preferred over similar preparations.

Adverse Reactions and Precautions

Systemic effects may result from absorption of local anesthetics, corticosteroids, and other ingredients from the mucosa of the anus and rectum or excoriated perianal skin. Sensitization may occur after the topical application of some drugs contained in these preparations. Symptoms of overdosage are uncommon because these drugs are used in small quantities.

ANUSOL
ANUSOL-HC

These mixtures are promoted for the relief of pain and pruritus associated with minor anorectal disorders. They supply some symptomatic relief, probably due to the presence of theobroma oil, vegetable oil base, zinc oxide, and hydrocortisone (in Anusol-HC) in the formulation, but they are not curative.

The hydrocortisone in Anusol-HC exerts an anti-inflammatory effect on acutely inflamed lesions, but prolonged treatment may cause undesirable systemic effects (see Chapter 35, Adrenal Corticosteroids).

USUAL DOSAGE.—

Anusol. *Rectal:* One suppository or the liberal application of ointment in the morning, at bedtime, and after each defecation.

Anusol-HC. *Rectal:* One suppository in the morning and at bedtime for three to six days or until the inflammation subsides. Therapy may be continued with the preparation without hydrocortisone.

PREPARATIONS.—

Anusol (Warner-Chilcott). *Rectal:* Ointment and suppositories containing bismuth subgallate 2.25%, bismuth resorcin compound 1.75%, benzyl benzoate 1.2%, Peruvian balsam 1.8%, zinc oxide 11%, and boric acid 5% in theobroma oil or hydrogenated vegetable oil (suppositories) base.

Anusol-HC (Warner-Chilcott). *Rectal:* Suppositories containing same formulation as Anusol suppositories plus hydrocortisone acetate 10 mg.

RECTAL MEDICONE
RECTAL MEDICONE-HC

These preparations are effective for the symptomatic relief of the pain and pruritus associated with minor anorectal disorders, but they are not curative. The mixtures combine a local anesthetic, antiseptic, emollient, protectant, and a corticosteroid (in Rectal Medicone-HC). The steroid, hydrocortisone acetate, exerts an anti-inflammatory effect on acutely inflamed lesions.

Undesirable systemic effects may result from prolonged treatment with Rectal Medicone-HC (see Chapter 35, Adrenal Corticosteroids).

USUAL DOSAGE.—

Rectal Medicone. *Rectal:* One suppository or the liberal application of ointment in the morning, at bedtime, and after each defecation.

Rectal Medicone-HC. *Rectal:* One suppository in the morning and at bedtime for three to six days. Therapy may be continued with the preparation without hydrocortisone.

PREPARATIONS.—

Rectal Medicone (Medicone). *Rectal:* Each gram of ointment contains benzocaine 20 mg, oxyquinoline sulfate 5 mg, menthol 4 mg, zinc oxide 100 mg, Peruvian balsam 12.5 mg, petrolatum 625 mg, and lanolin 210 mg; each suppository contains benzocaine 130 mg, oxyquinoline sulfate 16.2 mg, zinc oxide 194 mg, menthol 9 mg, and Peruvian balsam 65 mg in theobroma oil and vegetable and petroleum oil base.

Rectal Medicone-HC (Medicone). *Rectal:* Each suppository contains the same formulation as Rectal Medicone suppositories plus hydrocortisone acetate 10 mg.

WYANOIDS
WYANOIDS HC

These mixtures are marketed for the relief of pain and pruritus associated with minor anorectal disorders. They supply some symptomatic relief, probably due to the effects of zinc oxide, theobroma oil, and hydrocortisone (in Wyanoids HC) in the formulations. However, they also contain belladonna for no discernible reason. The manufacturer's labeling includes a dire warning about the possible toxic effects from absorption of the belladonna alkaloids if an excessive amount is used.

Undesirable systemic effects may occur after prolonged treatment with Wyanoids HC (see Chapter 35, Adrenal Corticosteroids).

USUAL DOSAGE.—Use of this preparation is inadvisable because of possible toxic effects mentioned above. The manufacturer's suggested dosages are:

Wyanoids. *Rectal:* One suppository at bedtime.

Wyanoids HC. *Rectal:* One suppository twice daily for six days as required.

PREPARATIONS.—

Wyanoids (Wyeth). *Rectal:* Each suppository contains belladonna extract 15 mg, ephedrine sulfate 3 mg, zinc oxide 176 mg, boric acid 543 mg, bismuth oxyiodide 30 mg, bismuth subcarbonate 146 mg, and Peruvian balsam 30 mg in theobroma oil and beeswax.

Wyanoids HC (Wyeth). *Rectal:* Each suppository contains same formulation as Wyanoids plus hydrocortisone acetate 10 mg.

Additional Mixtures

The following mixtures may provide symptomatic relief in some cases. However, inclusion in the list does not imply a recommendation for use; their ingredients should be evaluated in the light of the introduction to this chapter.

'A and D' Hemorrhoidal Suppositories (Schering): Each suppository contains vitamin A 1,500 units and vitamin D 200 units with Peruvian balsam, bismuth subgallate, and zinc oxide in an emollient base of theobroma oil, spermaceti, carnauba wax, and polysorbate 80 (with and without hydrocortisone acetate 10 mg).

Americaine (Arnar-Stone): Ointment containing benzocaine 20% and benzethonium chloride 0.1%.

Anugesic (Warner-Chilcott): Each gram of ointment contains pramoxine hydrochloride 10 mg, bismuth subgallate 22.5 mg, bismuth resorcin compound 17.5 mg, benzyl benzoate 12 mg, Peruvian balsam 18 mg, zinc oxide 107.5 mg, and boric acid 50 mg; each suppository contains pramoxine hydrochloride 25 mg, bismuth subgallate 61 mg, bismuth resorcin compound 47 mg, benzyl benzoate 32.4 mg, Peruvian balsam 48.6 mg, zinc oxide 300 mg, and boric acid 125 mg.

Cort-Dome (Dome): Each suppository contains hydrocortisone acetate 15 or 25 mg in a monoglyceride base.

Diothane (Merrell-National): Ointment containing diperodon 1% and oxyquinoline benzoate 0.1%.

Dorana (Ives): Each suppository or 30 mg of ointment contains phenylmercuric nitrate 1:10,000, shark liver oil 3%, and skin respiratory factor from yeast cells 2,000 units.

Epinephricaine (Upjohn): Ointment containing epinephrine 0.2%, secondary-amyltricresols 1%, zinc

oxide 2%, and benzocaine 2.5% in a bland base containing vitamins A and D.

Gentz (Philips Roxane): Jelly and wipes containing pramoxine hydrochloride 1%, alcloxa 0.2%, cetylpyridinium chloride 0.5%, and hamamelis water 50%.

MediConet (Medicone): Wipes impregnated with benzalkonium chloride, ethoxylated lanolin, methylparaben, hamamelis water, and glycerin.

Metycaine & Zinc Oxide Compound (Lilly): Each suppository contains piperocaine hydrochloride 125 mg, belladonna extract 0.125 mg, bismuth subcarbonate 125 mg, and zinc oxide 250 mg.

Nupercainal (Madison): Ointment containing dibucaine 1% in lanolin and petrolatum; suppositories containing dibucaine 2.5% in zinc oxide, bismuth subgallate, and theobroma oil.

P N S Suppositories (Winthrop): Each suppository contains tetracaine hydrochloride 10 mg, phenylephrine hydrochloride 5 mg, tyloxapol 25 mg, and bismuth subcarbonate 100 mg.

Proctodon (Rowell): Each gram of cream contains diperodon hydrochloride 1%, vitamin A palmitate 5,000 units, and vitamin D 1,000 units in a water-miscible base.

Proctofoam-HC (Reed & Carnrick): Foam containing pramoxine hydrochloride 1% and hydrocortisone acetate 1% in a water-soluble mucoadhesive base.

Proctoform (Fellows-Testagar): Each suppository contains bismuth subiodide 8 mg, bismuth subcarbonate 58.5 mg, zinc oxide 162.4 mg, boric acid 259 mg, isobutyl-p-aminobenzoate 65 mg in theobroma oil, spermaceti, and petrolatum.

Rectalgan Liquid (Ayerst): Liquid containing benzocaine 4.5%, benzethonium chloride 0.1%, phenol 0.05%, 8-hydroxyquinoline benzoate 1.2%, menthol 0.5%, and methylparaben 2% with isopropyl alcohol and soya bean and castor oils.

Rectodyne (Beecham-Massengill): Each 30 mg of ointment contains tetracaine hydrochloride 130 mg, powdered opium 130 mg, and stramonium extract 324 mg with phenol, tannic acid, hamamelis water, Peruvian balsam, thymol, and resorcinol; each suppository contains powdered opium 0.38% and belladonna extract 1% with benzocaine, boric acid, ammonium alum, and theobroma oil.

Tanicaine (Upjohn): Each 30 mg of ointment contains phenacaine hydrochloride 324 mg, atropine 16.2 mg, tannic acid 1.6 g, phenol 390 mg, camphor 454 mg, menthol 130 mg, and zinc oxide 5.2 g.

Xylocaine Suppositories (Astra): Each suppository contains lidocaine 100 mg, aluminum subacetate 75 mg, Peruviam balsam 100 mg, bismuth subgallate 115 mg, and zinc oxide 375 mg in neutral glycerides of saturated vegetable fatty acids.

Chapter 83

MISCELLANEOUS GASTROINTESTINAL AGENTS

The gastrointestinal agents described in this chapter are activated charcoal, simethicone, and products intended as replacement therapy in deficiency states (hydrochloric acid, glutamic acid hydrochloride, pepsin, bile acids and salts, and pancreatic enzymes).

The carminatives, which are often aromatic oils of vegetable origin and are given to relieve the feeling of distention after meals, as well as the stomachics (eg, bitters), which are claimed to enhance the functional activity of the stomach, are not discussed in this chapter. These drugs primarily exert a psychic or placebo effect, and the effectiveness of therapy may not be related to their pharmacologic actions. These agents were used much more frequently in the past than at present.

ACTIVATED CHARCOAL

This absorbent was once widely used to treat diarrhea, because it was believed that the presumed toxins adhered to its surfaces. It is now used as an adjunct in the treatment of oral poisonings caused by ingestion of heavy metals, some alkaloids, aniline dyes, and most drugs except cyanide. Contrary to popular belief, burnt toast is not a form of activated charcoal and is useless in the treatment of poisonings.

USUAL DOSAGE.—*Oral: Adults and children,* 1 to 10 g. For emergency treatment, the powder, stirred into water to give a slurry, can be administered and removed soon afterward by gastric tube or by induced vomiting. Alternatively, the charcoal suspension can be used as the gastric lavage fluid.

PREPARATIONS.—Activated Charcoal, U.S.P. *Oral:* Powder, capsules, and tablets. Drug marketed by many manufacturers under generic name.

SIMETHICONE [Mylicon, Silain]

This mixture of dimethylpolysiloxanes and silica gel is promoted for the relief of gaseous distention occurring postoperatively and as a result of aerophagia. However, there are no well-designed, controlled studies to support these claims; thus, the efficacy of simethicone is questionable. The claim is also made that simethicone is useful in the preparation of patients for gastroscopy to eliminate mucus-embedded bubbles that might interfere with the procedure. Since gas bubbles are seldom a problem during gastroscopy, the claim is not a convincing one. Silicon polymers are used in industry as defrothing agents because of their ability to lower surface tension.

No adverse reactions have been reported.

USUAL DOSAGE.—No useful dosage is recognized because evidence of efficacy is lacking. The manufacturers' suggested dosage is: *Oral: Adults,* 40 to 100 mg four times a day (after meals and at bedtime) or as necessary postoperatively.

PREPARATIONS.—

Mylicon (Stuart). *Oral:* Drops 40 mg/0.6 ml; tablets 40 mg.

Silain (Robins). *Oral:* Tablets 50 mg.

HYDROCHLORIC ACID, DILUTED

Hydrochloric acid was once commonly administered to alleviate symptoms such as epigastric distress after meals, abdominal distention, nausea, vomiting, diarrhea, and coated tongue supposedly associated with achlorhydria and hypochlorhydria. However, there is no proof that a decrease in the hydrochloric acid content of the stomach produces any specific symptoms. The usual therapeutic dose is not sufficient to cause free acid to appear in the stomach and there is no evidence that even large doses of hydrochloric acid are beneficial.

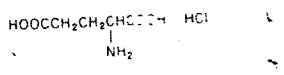
Large doses of 10 ml (30 mEq) given during

and after each meal in an attempt to approach the amount of acid normally secreted in response to a meal may produce metabolic acidosis. Alkalizing salts should be taken concurrently. The hydrochloric acid solution must be diluted with water and taken through a glass tube to prevent damage to the dental enamel.

USUAL DOSAGE.—No useful dosage is recognized because proof of efficacy is lacking. The manufacturers' suggested dosage is: *Oral: Adults*, 5 ml (15 mEq) of 10% hydrochloric acid, well diluted in water, taken at mealtime.

PREPARATIONS.—Hydrochloric Acid, Diluted, N.F. Marketed by many manufacturers under generic name.

GLUTAMIC ACID HYDROCHLORIDE
[Acidulin]



The proposed uses for this preparation are the same as those for diluted hydrochloric acid but, as with the free acid, there is no sound evidence that this drug has any more than a placebo effect. Capsules or tablets of glutamic acid hydrochloride are prescribed instead of free hydrochloric acid to prevent damage to the dental enamel. This drug does not lower the gastric pH as much as the free acid.

USUAL DOSAGE.—No useful dosage is recognized. The manufacturers' suggested dosage is: *Oral: Adults*, 340 mg to 1 g three times daily before meals.

PREPARATIONS.—Acidulin (Lilly). *Oral:* Capsules 340 mg. Drug also marketed by other manufacturers under generic name.

PEPSIN

This preparation of gastric enzymes is derived from hog stomach. The action of pepsins is not essential to digestion since the proteolytic enzymes of the intestinal tract can convert proteins to peptides and amino acids. Therefore, pepsin is not useful therapeutically.

USUAL DOSAGE.—Suggested dosage from the literature is: *Oral: Adults*, 10 to 30 ml of elixir or 2 g of powder or granules taken with meals three times daily.

PREPARATIONS.—*Oral:* Elixir (plain or lactated), granules, and powder.

AVAILABLE TRADEMARK.—Peptenzyme Elixir (Reed & Carnrick). Drug also marketed by other manufacturers under generic name.

BILE AND BILE ACIDS OR SALTS

The major bile acids are cholic, chenodeoxycholic, and deoxycholic acids. The first two are primary bile acids formed from cholesterol in the liver, and the latter is a secondary acid produced by the action of anaerobic intestinal bacteria on cholic acid. Normally, the bile acids do not occur in bile as free substances but as conjugates with taurine or glycine. Conjugated bile acids are also known as bile salts.

Bile salts pass from the liver into the intestine, where they enhance the absorption of lipids and are necessary for the absorption of fat-soluble vitamins and cholesterol. They are absorbed mainly by the ileum, return to the liver by way of the portal vein, and are reused, thus completing the enterohepatic circulation. Bile salts also regulate the synthesis of bile acid from cholesterol and the secretion of free cholesterol from the liver.

Many conditions (eg, fistula, resection or disease of the ileum, severe liver disease, biliary obstruction, bacterial overgrowth in the small intestine) interrupt the enterohepatic circulation and consequently reduce the concentration of conjugated bile salts in the upper intestine. At present, there is no satisfactory preparation of conjugated bile salts available for replacement therapy. Commercial ox bile preparations do not provide an adequate amount of conjugated bile salts and often cause diarrhea. Their use for replacement therapy or as choleretics in the treatment of various vague symptoms attributed to a deficiency of bile or to intestinal malfunction is not justified, for they are not effective and may be harmful in some instances.

Because bile salts are important for the normal biliary solubilization of cholesterol, disorders of bile acid metabolism may result in the production of abnormal bile and, thereby, cause cholesterol gallstone formation. Recently, reports have suggested that the long-term daily administration of 1 g of chenodeoxycholic acid, one of the primary bile acids, can reduce the size or completely dissolve cholesterol gallstones in selected, asymptomatic patients. There was no decrease in the size of gallstones in patients given cholic acid or placebo therapy.

OX BILE EXTRACT

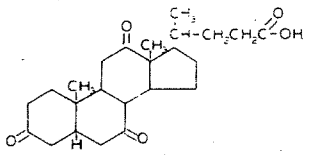
This is an ineffective preparation proposed for replacement therapy in patients who have an insufficient concentration of bile salts in the intestine. See the introduction to this section.

Diarrhea may occur after use of ox bile extract.

USUAL DOSAGE.—The manufacturers' suggested dosage is: *Oral: Adults*, 300 mg.

PREPARATIONS.—Ox Bile Extract. *Oral:* Capsules, tablets. Drug marketed under generic name.

DEHYDROCHOLIC ACID [Decholin]
DEHYDROCHOLATE SODIUM [Decholin Sodium]



Dehydrocholic acid, a synthetic derivative of cholic acid, is the most active of the hydrocholeretics. Since this drug increases the volume of bile by dilution without increasing the total solids, it is used postoperatively to increase the flow and reduce the viscosity of bile during T-tube drainage. However, there is no evidence to support the claim that hydrocholeretics prevent ascending infection in biliary tract disease or after surgery.

Dehydrocholic acid also is sometimes used to dislodge small calculi from the biliary tract; however, if the calculi are not dislodged and become impacted, an attack of biliary colic may occur. A smooth muscle relaxant, such as a nitrite, may be given with the hydrocholeretic.

Hydrocholeresis may assist in outlining bile ducts to determine obstruction and may improve gallbladder visualization in x-ray diagnosis.

The sodium salt is given intravenously to measure circulation time, since the drug creates a bitter taste when it reaches the tongue.

Anaphylactic reactions occur infrequently.

USUAL DOSAGE.—

Dehydrocholic Acid:

Oral: Adults, 500 mg three times daily.

Dehydrocholate Sodium:

Intravenous: Adults (diagnostic), 3 to 5 ml of a 20% solution.

PREPARATIONS.—

Decholin (Dome). *Oral:* Tablets 250 mg.

Decholin Sodium (Dome). *Injection:* Solution 20% in 5 ml containers.

ADDITIONAL TRADEMARKS.—**Dehydrocholic Acid:** Bili (Reid-Provident), Cholan-DH (Pennwalt), Ketochol (Searle). Both forms also marketed by other manufacturers under generic names.

PANCREATIC ENZYMES

The pancreatic enzymes (amylase, trypsin, and lipase) are obtained from various preparations of hog pancreas. They are effective in patients whose exocrine pancreatic secretion is deficient. Thus, they may be used as replacement therapy in chronic pancreatitis, in ductal obstruction caused by cancer of the pancreas, in cystic fibrosis, and after pancreatectomy. However, these enzymes should be used only after the diagnosis of exocrine pancreatic insufficiency has been established. They are ineffective in gastrointestinal disorders unrelated to pancreatic enzyme insufficiency.

Some preparations are enteric coated to avoid destruction of variable amounts by gastric pepsin.

Although allergic reactions to the animal protein in these preparations occur only rarely, these enzymes should be used cautiously in patients known to be sensitive to pork.

The dosage depends upon the condition of the patient, the amount of fat in the diet, and the qualitative enzyme content of each preparation.

PANCREATIN [Panteric, Viokase]

These preparations of pancreatin are derived from hog pancreas and contain amylase, trypsin, lipase, and other constituents in varying amounts. The N.F. preparation of pancreatin must convert at least 25 times its weight of starch into soluble carbohydrates and of casein into proteoses. The required lipolytic activity is not specified. Preparations containing three or four times N.F. strength also are available.

See the introduction to this section for indications and precautions.

USUAL DOSAGE.—*Oral: Adults*, 4 to 12 g (triple N.F. strength) daily in divided doses at one- or two-hour intervals or before and after meals with an extra dose taken with any food eaten between meals; *children*, initially, 300 to 600 mg with each meal. This dose may be increased if necessary if no nausea, vomiting, or diarrhea occurs.

PREPARATIONS.—

Pancreatin (Lilly). *Oral:* Powder; tablets (enteric-coated) 325 mg (three times N.F. strength); tablets 325 mg (N.F. strength).

Panteric (Parke, Davis). *Oral:* Capsules 325 mg (three times N.F. strength); granules; tablets (enteric-coated) 325 mg (three times N.F. strength).

Viokase (Viobin). *Oral:* Powder; tablets 325 mg (four times N.F. strength).

Drug also marketed by other manufacturers under generic name.

PANCRELIPASE [Cotazym]

The action of pancrelipase is qualitatively similar to that of other pancreatic enzyme preparations; however, it has greater lipase activity as determined by in vitro measurements of the amount of glycerin (free fatty acids) formed by the digestion of fat. This greater lipase activity permits smaller doses to be used to help control steatorrhea. Although pancrelipase may be more acceptable to patients because of the smaller dosage, there are no controlled clinical and metabolic studies to determine the relative efficacy of the various pancreatic enzyme preparations.

See the introduction to this section for indications and precautions.

USUAL DOSAGE.—*Oral: Adults*, 300 to 900 mg with each meal depending upon the amount of fat ingested, and 300 mg with any food eaten between meals. *Children*, 300 to 600 mg with each meal. In severe deficiency, doses of 1 g every waking hour have been given.

PREPARATIONS.—Cotazym (Organon). *Oral:* Capsules 300 mg; powder 600 mg and 1.5 g. Each 300 mg capsule provides: lipase sufficient to digest 17 g dietary fat; trypsin sufficient to digest 34 g dietary protein; and amylase sufficient to digest 40 g dietary starch (based on in vitro assays).

MIXTURES

The following mixtures containing bile constituents and derivatives, enzymes, sedatives, antispasmodics, cellulase, and other ingredients are marketed for the treatment of many ill-defined gastrointestinal syndromes. There are no therapeutic indications for ox bile, pepsin, and hydrocholic acid. Pancreatic enzymes are indicated only when a demonstrated exocrine pancreatic deficiency exists, in which case the pancreatic enzymes should be prescribed alone. Other active ingredients of these mixtures (eg, sedatives, antispasmodics) should be prescribed separately and not in combination with useless drugs or ones whose use is not warranted.

Accelerase (Organon): Each capsule contains pancrelipase approximately 165 mg, mixed conjugated bile salts 65 mg, cellulase 2 mg, and calcium carbonate 20 mg.

Accelerase-PB (Organon): Each capsule contains pancrelipase approximately 165 mg, mixed conjugated bile salts 65 mg, cellulase 2 mg, calcium carbonate 20 mg, belladonna alkaloids as sulfates 0.2 mg, and phenobarbital 16 mg.

Acidol-Pepsin (Winthrop): Each capsule contains betaine hydrochloride 260 mg and pepsin 230 mg.

Bilogen (Organon): Each tablet contains ox bile extract 120 mg, oxidized mixed ox bile acids 75 mg, desoxycholic acid 30 mg, and pancreatin 250 mg.

Bilron (Lilly): Each capsule contains bile salts and iron.

Butibel-Zyme (McNeil): Each tablet contains proteolytic enzyme standardized 10 mg, amylolytic enzyme standardized 20 mg, cellulolytic enzyme standardized 5 mg, lipolytic enzyme standardized 100 mg, iron ox bile 30 mg, butabarbital sodium 15 mg, and belladonna extract 15 mg.

Caripeptic (Upjohn): Each 100 ml of liquid contains standard enzymes of *Carica papaya* with diastase 3.97 g, and alcohol 18%.

Chobile (Mallinckrodt): Each tablet contains ox bile extract 216.4 mg and oxidized ox bile acids 97.4 mg.

Chobile Pan (Mallinckrodt): Each tablet contains ox bile 216.4 mg, oxidized ox bile acids 97.4 mg, and pancreatin 97.4 mg.

Cholan HMB (Pennwalt): Each tablet contains dehydrocholic acid 250 mg, phenobarbital 8 mg, and homatropine methylbromide 2.5 mg.

Cholan V (Pennwalt): Each tablet contains dehydrocholic acid 250 mg and homatropine methylbromide 5 mg.

Choleo-Caps (Smith, Miller & Patch): Each capsule contains ox bile extract 24.3 mg, iron lactate 48.6 mg, calumba 48.6 mg, chamomile 105.5 mg, and rhubarb 105.5 mg.

Convertin (Ascher): Each tablet contains betaine hydrochloride 130 mg and oleoresin ginger 0.1 mg (in outer layer); pancreatin 250 mg and desoxycholic acid 50 mg (in enteric-coated core).

Convertin-H (Ascher): Each tablet contains betaine hydrochloride 130 mg and oleoresin ginger 0.1 mg (in outer layer); pancreatin 250 mg, desoxycholic acid 50 mg, and homatropine methylbromide 2.5 mg (in enteric-coated core).

Converzyme (Ascher): Each 5 ml of liquid contains proteolytic enzyme 10 mg, amylolytic enzyme 80 mg, sorbitol 4.4 g, and homatropine methylbromide 2.5 mg.

Cotazym-B (Organon): Each tablet contains lipase 1,000 units; trypsin, amylase, and other pancreatic enzymes; mixed conjugated bile salts 65 mg; and cellulase 2 mg.

Dactilase (Lakeside): Each tablet contains cellulolytic enzyme 2 mg, amylolytic enzyme 15 mg, proteolytic enzyme 10 mg, pancreatin 100 mg (3 X N.F.), piperidolate hydrochloride 50 mg, and taurocholic acid 15 mg.

Decholin-BB (Dome): Each tablet contains dehydrocholic acid 250 mg, belladonna extract 10 mg, and butabarbital sodium 15 mg.

Decholin with Belladonna (Dome): Each tablet contains dehydrocholic acid 250 mg and belladonna extract 10 mg.

Di-Gel (Plough): Each tablet or 5 ml contains simethicone 25 mg and magnesium carbonate.

Digolase (Boyle): Each capsule contains pancreatin concentrate 80 mg (3 X N.F.), amylase concentrate 15 mg, proteinase concentrate 3 mg, and polysorbate 80, 20 mg.

Donnazyme (Robins): Each tablet contains pepsin 150 mg, pancreatin 300 mg, bile salts 150 mg, hyoscyamine sulfate 0.0518 mg, atropine sulfate 0.0097 mg, hyoscine hydrobromide 0.0033 mg, and phenobarbital 8.1 mg.

Doxegest (Breon): Each tablet contains desoxycholic acid 32.5 mg, papain 15 mg, pancreatin 87.5 mg (3 X N.F.), hemicellulase 25 mg, ketocholanic acid 12.5 mg, and betaine hydrochloride 65 mg.

Doxychol-AS (Cooper): Each tablet contains desoxycholic acid 64.8 mg, dehydrocholic acid 194 mg, hyoscyamine hydrobromide 0.16 mg, phenobarbital 8 mg, and atropine sulfate 0.16 mg.

Desoxychol-K (Cooper): Each tablet contains desoxycholic acid 64 mg and dehydrocholic acid 194 mg.

Entozyme (Robins): Each tablet contains pepsin 250 mg (in outer layer); pancreatin 300 mg and bile salts 150 mg (in enteric-coated core).

Festal (Hoechst): Each enteric-coated tablet contains pancreatic lipase 10 Willstaetter units (WU), pancreatic amylase 10 WU, pancreatic protease 17 WU, hemicellulase 50 mg, and bile constituents 25 mg.

Festalan (Hoechst): Each tablet contains lipase 10 Willstaetter units (WU), amylase 10 WU, protease 17 WU, hemicellulase 50 mg, and bile constituents 25 mg (in enteric-coated core); atropine methylnitrate 1 mg (in outer layer).

Gastroenterase (Wampole): Each tablet contains pepsin 150 mg (in outer layer); pancreatic enzyme concentrate 100 mg, cellulase 25 mg, dehydrocholic acid 50 mg (in enteric-coated core).

Hydro-Bilein (Abbott): Each tablet contains ox bile extract 120 mg and dehydrocholic acid 120 mg.

Hydrochol Plus (Elder): Each tablet contains dehydrocholic acid 200 mg, ox bile 50 mg, methscopolamine nitrate 0.8 mg, and amobarbital 15 mg.

Kanulase (Dorsey): Each tablet contains pepsin N.F. 150 mg, cellulase 9 mg, glutamic acid hydrochloride 200 mg, pancreatin N.F. 500 mg, and ox bile extract 100 mg.

Kanumodic (Dorsey): Each tablet contains pepsin N.F. 150 mg, cellulase 9 mg, glutamic acid hydrochloride 200 mg, pancreatin N.F. 500 mg, ox bile extract 100 mg, pentobarbital 8 mg, and methscopolamine nitrate 2 mg.

Ketosox (Ascher): Each tablet contains desoxycholic acid 65 mg and ketocholanic acids 200 mg.

Kutrase (Kremers-Urban): Each capsule contains phenyltoloxamine citrate 15 mg, hyoscyamine sulfate 0.0625 mg, amylolytic enzyme 30 mg, proteolytic enzyme 6 mg, lipolytic enzyme 75 mg, and cellulolytic enzyme 2 mg.

Ku-Zyme (Kremers-Urban): Each capsule contains amylolytic enzyme 30 mg, proteolytic enzyme 6 mg, lipolytic enzyme 75 mg, and cellulolytic enzyme 2 mg.

Maturon (Ayerst): Each tablet contains amylase 3,000 units, protease 12,000 units, tryptic activity 500 units, dehydrocholic acid 40 mg, vitamin A 2,500 U.S.P. units, ergocalciferol 125 U.S.P. units, ascorbic acid 25 mg, thiamine mononitrate 1.5 mg, riboflavin 1 mg, pyridoxine hydrochloride 0.5 mg, cyanocobalamin 0.5 μg, calcium pantothenate 3.5 mg, nicotinamide 7.5 mg, vitamin E 2.5 IU, calcium 35 mg, phosphorus 27 mg, iron 12.5 mg, manganese 0.15 mg, zinc 0.2 mg, magnesium 2.5 mg, and inositol 10 mg.

Neocholan (Dow): Each tablet contains dehydrocholic acid 250 mg, bile extract 15 mg, phenobarbital 8 mg, and homatropine methylbromide 1.2 mg.

Normacid (Stuart): Each tablet contains pepsin 100 mg and betaine hydrochloride 440 mg.

Nu Leven (Lemmon): Each enteric-coated tablet contains pepsin 150 mg, pancreatic enzyme concentrate 100 mg, and ox bile extract 100 mg.

Oxsorbil (Ives): Each capsule contains dehydrocholic acid 32.4 mg, desoxycholic acid 32.4 mg, ox bile extract 65 mg, oleic acid 178.6 mg, and polysorbate 80, 162.4 mg.

Oxsorbil-PB (Ives): Each capsule contains dehydrocholic acid 32.4 mg, desoxycholic acid 32.4 mg, ox bile extract 65 mg, oleic acid 178.6 mg, phenobarbital 8.1 mg, belladonna powder extract 8.1 mg, and polysorbate 80, 162.4 mg.

Panteric Compound (Parke, Davis): Each tablet contains pancreatin 650 mg (3X equivalent to pancreatin N.F.) and ox bile extract N.F. 97.4 mg.

AMA DRUG EVALUATIONS

Paptose (First Texas): Each 30 ml of liquid contains diastase 40 mg, papain 389 mg, rennin 40 mg, and alcohol 15%.

Phazyme (Reed & Carnrick): Each tablet contains pepsin N.F. 100 mg, diastase 25 mg, activated simethicone 20 mg, with and without phenobarbital 15 mg (in outer layer); pancreatin 240 mg and activated simethicone 40 mg (in enteric-coated core).

Pradase (Cooper): Each tablet contains ox bile extract N.F. 150 mg, ketocholanic acid 60 mg, pancreatin N.F. 300 mg, betaine hydrochloride 90 mg, and carminative oils 0.006 ml.

Ro-Bile (Rowell): Each tablet contains pepsin N.F. 260 mg (in outer layer); enzyme concentrate 75 mg (pancreatin 4X N.F. with added standardized lipase), ox bile extract N.F. 100 mg, dehydrocholic acid U.S.P. 30 mg, and belladonna extract N.F. 8 mg (in enteric-coated core).

Sidonna (Reed & Carnrick): Each tablet contains simethicone 25 mg, hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, scopolamine hydrobromide 0.0065 mg, and sodium butabarbital 16 mg.

Silain-Gel (Robins): Each tablet contains simethicone 25 mg, aluminum hydroxide-magnesium carbonate co-dried 282 mg, and magnesium hydroxide 85 mg.

Supligol (Breon): Each enteric-coated tablet contains dessicated whole bile 260 mg and ketocholanic bile acids 65 mg.

Taka-Diastase, Pepsin, and Pancreatin (Parke, Davis): Each tablet contains *Aspergillus oryzae* enzymes 130 mg, pepsin 65 mg, and pancreatin 130 mg.

Therabile (Ascher): Each tablet contains desoxycholic acid 25 mg, ferrated ox bile 200 mg, pancreatin N.F. 250 mg, homatropine methylbromide 2.5 mg, oleoresin ginger 0.1 mg, and dimethionine 100 mg.

Trienzyme (Fellows-Testagar): Each tablet contains amylolytic enzyme 30 mg, proteolytic enzyme 10 mg, and cellulolytic enzyme 3 mg.

Trulase (Cooper): Each tablet contains amylolytic enzyme 30 mg, proteolytic enzymes 6 mg, and lipolytic enzyme 25 mg.

Zymogest (Amfre-Grant): Each tablet contains standardized amylolytic enzyme 25 mg, standardized proteolytic enzyme 10 mg, standardized cellulolytic enzyme 1 mg, dehydrocholic acid 100 mg, hyoscyamine hydrobromide 0.1 mg, hyoscine hydrobromide 0.0065 mg, and atropine sulfate 0.02 mg.

Chapter 84

EMETICS

Emetics (eg, apomorphine hydrochloride, ipecac syrup) are used to induce vomiting after the ingestion of poisons. Small doses of emetics also have been tried with varying degrees of success as a deterrent in chronic alcoholism. Their use as expectorants, usually in about one-fifth the emetic dose, in the treatment of childhood croup, bronchitis, bronchiectasis, asthma, or other conditions associated with unproductive coughing is no longer recommended, for these agents may suppress the appetite and make fluid ingestion and retention difficult. (See Chapter 43, Expectorants and Inhalants.)

Vomiting can be elicited by a direct action of an emetic on the chemoreceptor trigger zone in the medulla, by indirect stimulation of the gastrointestinal tract, or by a combination of these effects. The effectiveness of emetics may be facilitated by having the patient drink 200 to 300 ml of water concomitantly.

Although there is universal agreement that emptying the stomach completely after ingestion of most poisons is desirable, there is disagreement on whether properly performed gastric lavage or drug-induced vomiting is the more effective method. Most of the ingested material still in the stomach is usually recovered with use of an emetic. Although the act of inserting the tube may cause vomiting, especially in children, emptying of the stomach in this way is thought to be less efficient than drug-induced vomiting. Aspiration of vomitus into the bronchial tree also is a potential hazard of both gastric lavage and drug-induced vomiting but the hazard is less with use of emetics.

Antimony potassium tartrate (tartar emetic) and mustard powder have been used as emetics, but the former is too toxic and the latter agent is ineffective. Cupric sulfate is effective, but its potential toxicity is too great to recommend its use.

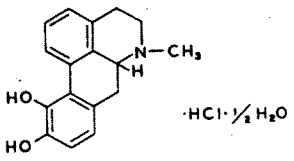
Adverse Reactions and Precautions

Emetics are contraindicated in patients who are unconscious or semicomatose, inebriated, or in shock. An emetic should not be used if the patient has ingested a caustic substance, since additional injury to the esophagus and possible mediastinitis may result. Gastric lavage would be the treatment of choice if an antiemetic has been ingested recently.

Emetics are generally contraindicated after ingestion of petroleum distillates (eg, kerosene, gasoline) or volatile oils because the patient may aspirate these substances into the bronchial tree while retching and vomiting, and bronchospasm, pulmonary edema, or pneumonia may result. However, definitive data are lacking to indicate that use of an emetic in an alert patient increases the probability of aspiration pneumonia. Some authorities believe that prompt and complete emptying of the stomach achieved by careful aspiration and lavage is effective; when the patient is comatose, a cuffed endotracheal tube is used whenever possible to prevent aspiration. Others prefer that a vegetable oil (eg, corn oil, peanut oil) be given to delay absorption of accidentally ingested petroleum distillates. Neither point of view is established as being superior. The same quantity of petroleum distillates aspirated into the lungs has many times the toxicity it has in the stomach. Thus, in cases of ingestion of known small quantities of petroleum distillates, it is safer to allow the material to remain in the stomach without removal rather than to introduce the risk of aspiration. However, when a petroleum distillate is a solvent for a toxic substance (eg, insecticide) the benefits of employing gastric lavage far outweigh the risks.

INDIVIDUAL EVALUATIONS

APOMORPHINE HYDROCHLORIDE



Apomorphine acts directly on the chemoreceptor trigger zone and usually induces vomiting in most adults within five to ten minutes after subcutaneous injection. Generally, the stomach contents are expelled completely and may even contain reflux from the upper intestinal tract. Its action is more efficient when the stomach is full; therefore, 200 to 300 ml of water should be given just before the injection.

Apomorphine usually produces some depression of the central nervous system, but some patients may experience euphoria, restlessness, and tremors. It may produce acute circulatory failure in aged or debilitated patients. Larger or repeated doses *depress* the respiratory center. Overdosage may produce violent vomiting, retching, acute circulatory failure, and death. The depressant actions of apomorphine usually can be reversed by a narcotic antagonist (0.02 mg/kg of body weight of levallorphan, 0.1 mg/kg of nalorphine, or 0.005 mg/kg of naloxone). The narcotic antagonist usually is unnecessary but some physicians administer it routinely to terminate vomiting and alleviate drowsiness. Activated charcoal should be administered orally when an adsorbable substance has been ingested after apomorphine is injected or before if delay in the administration of the emetic is anticipated. (See Chapter 83, Miscellaneous Gastrointestinal Agents.) Apomorphine is a Schedule II controlled drug.

Apomorphine is contraindicated after the ingestion of corrosive substances or alcohol. It also is contraindicated in patients in shock, in comatose or elderly patients, or in those sensitive to morphine derivatives. Apomorphine is not stable and should not be used if the solution is green or brown.

USUAL DOSAGE.—*Subcutaneous: Adults and children*, 0.1 mg/kg of body weight; 200 to 300 ml of water should be taken just before the injection.

PREPARATIONS.—Apomorphine Hydrochloride, N.F. *Injection:* Tablets (hypodermic) 6 mg. Drug marketed under generic name.

IPECAC SYRUP

Ipecac alkaloids act both locally on the gastric mucosa and on the chemoreceptor trigger zone to induce vomiting. An adequate dose causes vomiting in more than 90% of patients within 30 minutes; the average time is usually less than 20 minutes. The stomach is evacuated completely, along with reflux material from the upper intestinal tract. Ipecac syrup is available without prescription in a maximal amount of 30 ml and is labeled in accordance with the requirements of the FDA. This preparation should be available in the home for use in emergencies to avoid delay in treatment if a physician prescribes it by telephone. The emetic action is facilitated if the patient drinks 200 to 300 ml of water concomitantly.

Ipecac syrup should not be confused with ipecac fluidextract. The latter preparation is 14 times more concentrated and has caused several deaths. Fortunately, the fluidextract is no longer official, but it still may be available. Therefore, it is essential that the physician clearly specify ipecac syrup in prescribing and not use the single word "ipecac."

Ipecac syrup is contraindicated in patients who are unconscious, semicomatose, severely inebriated, or in shock. It should not be used if the patient has ingested a corrosive or caustic substance, since regurgitation may further injure the esophagus. It is contraindicated after ingestion of petroleum distillates (eg, kerosene, gasoline) or volatile oils. (See the Introductory Statement.)

Activated charcoal should not be given simultaneously with ipecac syrup, because the charcoal adsorbs the ipecac and nullifies its effect; however, it may be given after vomiting has occurred. (See Chapter 83, Miscellaneous Gastrointestinal Agents.)

USUAL DOSAGE.—*Oral: Adults*, 15 to 30 ml followed by 200 to 300 ml of water; *children over 1 year*, 15 ml followed by about 200 ml of water. Dose may be repeated once after 20 minutes if necessary.

PREPARATIONS.—Ipecac Syrup, U.S.P. Drug marketed under generic name.

Chapter 85

ANTIEMETICS

Vomiting is a complex act that is coordinated by the vomiting center in the medulla. Stimuli are relayed to the center from many peripheral areas (eg, gastric mucosa, peritoneum, joints, tendons), as well as from areas within the central nervous system itself (eg, vestibular apparatus of the ear, chemoreceptor trigger zone, cerebral cortex).

Antiemetic agents prevent or relieve nausea and vomiting by exerting their effects either on the aural vestibular apparatus, the chemoreceptor trigger zone, the cerebral cortex, or the vomiting center itself. Since their mechanism of action is not fully understood in all cases, the choice of drug is often empirical.

Nausea and vomiting may be symptoms of serious organic disturbances or may be produced by infections, drugs, radiation, painful stimuli, emotional disturbances, or motion. Whenever possible, the underlying cause should be determined and corrected. When vomiting accompanies a form of therapy, the use of antiemetics is justified as an adjunct to the treatment.

The selection of an antiemetic should be based upon the cause of the vomiting. Some compounds are effective in preventing or treating vomiting due to motion sickness but are ineffective in controlling vomiting due to other causes. Some agents also relieve vertigo due to labyrinthitis, surgery of the middle and inner ear, or Meniere's disease.

The types of antiemetics include: (1) sedatives and hypnotics (eg, phenobarbital), which act centrally by depressing the cerebral cortex or the vomiting center; (2) scopolamine, an anticholinergic agent, which appears to act primarily by reducing the excitability of the labyrinth receptors and by depressing conduction in the vestibular cerebellar pathways; (3) antihistamines (cyclizine [Marezine], dimenhydrinate [Dramamine], diphenhydramine [Benadryl], meclizine [Antivert, Bonine], hydroxyzine [Atarax, Vistaril]) are assumed to affect neural pathways originating in the labyrinth; (4) the phenothiazines, which act upon the chemoreceptor trigger zone, the vomiting center, or both, and (5) some miscellaneous agents (eg, diphenidol [Vontrol], trimethobenzamide [Tigan]), the former agent acting upon the aural vestibular apparatus and the latter agent acting upon the chemoreceptor trigger zone.

The butyrophenones (eg, droperidol [Inapsine], haloperidol [Haldol]), which are pharmacologically similar to the phenothiazines, also have antiemetic properties. (See also Chapter 20, Adjuncts to Anesthesia, and Chapter 29, Antipsychotic Agents.) Pyridoxine (vitamin B_6) has been used in the management of nausea and vomiting of pregnancy, but it is ineffective. (See Chapter 14, Vitamins and Sources of Vitamins.)

Although the phenothiazines are the most potent and effective antiemetics, they should be prescribed only when vomiting cannot be controlled by less hazardous agents. Those used most commonly for their antiemetic effect include chlorpromazine [Thorazine], fluphenazine [Permitil, Prolixin], perphenazine [Trilafon], prochlorperazine [Compazine], promethazine [Phenergan], thiethylperazine [Torecan], and trifluprom azine [Vesprin]. The phenothiazine antiemetics are effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins. They also are useful in controlling the intractable vomiting of terminal

patients with uremia. With the exception of promethazine, the phenothiazines are not useful in preventing or treating motion sickness.

The nonphenothiazine antiemetics are drugs of first choice, particularly for patients receiving long-term antiemetic therapy (eg, those with hyperemesis gravidarum or nausea due to malignancy or administration of antineoplastic agents). They may be less effective and have a shorter duration of action than the phenothiazines, but are safer.

Scopolamine is one of the most effective agents for the prevention of motion sickness. However, its use is limited because of untoward effects and short duration of action. Promethazine, cyclizine, meclizine, and diphenhydramine are less effective, but they have a longer duration of action and produce fewer untoward effects than scopolamine. In controlled studies with individuals who were subjected to severe motion, the combination of scopolamine and ephedrine or dextroamphetamine was shown to be more effective than scopolamine alone.

Routine administration of antiemetics to *prevent* postoperative vomiting may be justified only when vomiting endangers the results of surgery (eg, intraocular or intracranial operations) or when elderly cardiac patients or individuals who might be endangered by dehydration or postoperative electrolyte imbalance must undergo surgery.

These drugs should not be used unless absolutely necessary during pregnancy. If an antiemetic is indicated, one of the well-established antihistamines should be selected (eg, dimenhydrinate). If vomiting persists, consideration may be given to the use of a phenothiazine.

Adverse Reactions and Precautions

Caution is required in the use of antiemetics because they may mask an underlying organic disease or the toxic effects of other drugs.

Drowsiness is the commonest untoward effect and is produced by most antiemetic agents. Individuals whose activities require alertness, such as those operating vehicles or machinery, should use these agents with caution.

Some nonphenothiazine antiemetics (cyclizine [Marezine], hydroxyzine [Atarax, Vistaril], meclizine [Antivert, Bonine]) are teratogenic in animals when given in doses substantially above the therapeutic range in man. Therefore, the possibility that these drugs may be hazardous to the fetus must be borne in mind. (See the discussion on Use of Drugs During Pregnancy in the General Information section.)

Phenothiazines: Phenothiazines in the piperazine group (fluphenazine [Permitil, Prolixin], perphenazine [Trilafon], prochlorperazine [Compazine], and thiethylperazine [Torecan]) are less likely to cause drowsiness, orthostatic hypotension, dryness of the mouth, and nasal congestion than those in the aliphatic group (chlorpromazine [Thorazine], promazine [Sparine], promethazine [Phenergan], and triflupromazine [Vesprin]). Cholestatic jaundice, granulocytopenia, urticaria, dermatitis, thrombocytopenia, leukopenia, agranulocytosis, purpura, pancytopenia, and gastroenteritis also have occurred after use of the phenothiazines. Less common reactions include galactorrhea, photosensitivity, and edema of the extremities.

Extrapyramidal reactions, including dystonia, parkinsonian syndrome, akathisia, and dysphasia, have been associated with the use of all phenothiazines. The incidence of these reactions is higher with drugs in the *piperazine* group than with those in the *aliphatic* group. Drugs in the *piperidine* group (eg, thioridazine [Mellaril]) are least likely to cause extrapyramidal reactions, but they are not effective as antiemetics.

Phenothiazines are contraindicated in patients with a history of dyskinetic reactions or epilepsy or in pregnant women with preeclampsia.

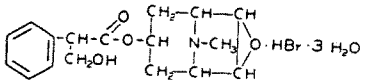
The additive effects (eg, sedation) that occur when phenothiazines are used with other central nervous system depressants should be borne in mind before an antiemetic of this type is given. The additive effect may be desirable in some patients (eg, those with malignancies) but is undesirable in others (eg, those under the influence of alcohol, barbiturates, or strong analgesics). Phenothiazines should not be given to patients who are somnolent or comatose, to those who exhibit other signs of central nervous system depression or hypotension, or to those receiving spinal or epidural anesthesia or adrenergic blocking agents.

Since phenothiazines are detoxified primarily in the liver, these agents should be used with caution in patients with liver dysfunction.

See also Chapter 29, Antipsychotic Agents.

NONPHENOTHIAZINE ANTIEMETICS

SCOPOLAMINE HYDROBROMIDE (Hyoscine Hydrobromide)



Scopolamine has a rapid onset and short duration of action (one-half to three hours). Although available evidence indicates that this is the most effective agent in the prevention or treatment of motion sickness, it has been largely supplanted by some of the newer antimotion sickness drugs, principally because of its untoward effects. Results of controlled studies with individuals in a selected age group who were subjected to severe motion indicate that there is a synergistic effect when 0.6 mg of scopolamine is given with 50 mg of ephedrine or 10 mg of dextroamphetamine.

Blurred vision, dryness of the mouth, vertigo, increased pulse rate, drowsiness, euphoria, amnesia, and fatigue are associated with use of scopolamine, especially in larger doses. Excitement, restlessness, hallucinations, or delirium also may occur.

For other uses, see Chapter 20, Adjuncts to Anesthesia, and Chapter 74, Antiparkinsonism Agents.

USUAL DOSAGE.—*Oral, Subcutaneous: Adults*, 0.6 to 1 mg; *children*, 0.006 mg/kg of body weight.

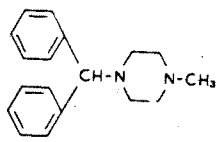
PREPARATIONS.—

Oral: Tablets 0.3, 0.4, and 0.6 mg.

Injection: Solution 0.3, 0.4, 0.5, 0.6, 0.8 mg/ml in 1 ml containers.

Drug marketed under generic name.

CYCLIZINE HYDROCHLORIDE [Marezine Hydrochloride]
CYCLIZINE LACTATE [Marezine Lactate]



Cyclizine, an antihistamine, is useful in preventing and relieving symptoms of motion sickness and postoperative nausea and vomiting. This drug also relieves vertigo and other symptoms of vestibular disorders of the ear. The duration of action of cyclizine is four to six hours.

Large doses may cause drowsiness and dryness of the mouth. See the Introductory Statement for a discussion on the drug's possible teratogenic effects when used during pregnancy.

USUAL DOSAGE.—

Cyclizine Hydrochloride:

Oral: For motion sickness, *adults*, 50 mg one-half hour before departure, then every four to six hours as necessary (maximal daily dose, 200 mg); *children*, 3 mg/kg of body weight divided into three doses during a 24-hour period.

Rectal: For motion sickness, *adults*, 100 mg three or four times daily as necessary; *children*, 6 mg/kg of body weight divided into three doses during a 24-hour period.

Cyclizine Lactate:

Intramuscular: Adults, for motion sickness, 50 mg three or four times daily as required. To prevent postoperative vomiting, 50 mg preoperatively or 20 to 30 minutes before expected termination of surgery; postoperatively, 50 mg every four to six hours if required. *Children*, for motion sickness, 3 mg/kg of body weight divided into three doses during a 24-hour period.

PREPARATIONS.—

Marezine [hydrochloride] (Burroughs Wellcome).

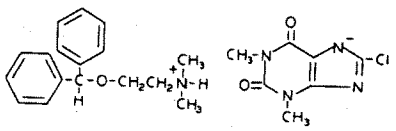
Oral: Tablets 50 mg.

Rectal: Suppositories 50 and 100 mg.

Marezine [lactate] (Burroughs Wellcome).

Injection: Solution 50 mg/ml in 1 ml containers.

DIMENHYDRINATE [Dramamine]



This chlorotheophylline salt of the antihistamine, diphenhydramine, is useful in preventing and treating motion sickness, nausea and vomiting during pregnancy, and postoperative nausea and vomiting. Its duration of action is four to six hours.

Mild drowsiness is associated with use of dimenhydrinate.

USUAL DOSAGE.—

Intramuscular: Adults, 50 mg as needed; *children*, 5 mg/kg of body weight divided into four doses during a 24-hour period (maximal dose, 300 mg/day).

Intravenous: Adults, 50 mg diluted in 10 ml of sodium chloride injection and injected over a

period of two minutes; *children*, no dosage has been established.

Oral, Rectal: Adults, 50 to 100 mg every four hours; *children*, 5 mg/kg of body weight divided into four doses during a 24-hour period (maximal dose, 300 mg/day).

PREPARATIONS.—Dramamine (Searle).

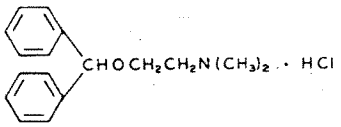
Injection: Solution 50 mg/ml in 1 and 5 ml containers.

Oral: Liquid 15 mg/5 ml; tablets 50 mg.

Rectal: Suppositories 100 mg.

ADDITIONAL TRADEMARKS.—Dimen (Robinson), Dimenest (Fellows-Testagar).

DIPHENHYDRAMINE HYDROCHLORIDE [Benadryl]



This antihistamine is similar to cyclizine in its actions. It is effective in the prevention and treatment of motion sickness, postoperative nausea, and nausea and vomiting of pregnancy. Its duration of action is four to six hours.

The incidence of drowsiness is high; vertigo has occurred occasionally. Individuals whose activities require alertness, such as those operating vehicles or machinery, should use diphenhydramine with caution.

For other uses, see Chapter 45, Antihistamines, and Chapter 74, Antiparkinsonism Agents.

USUAL DOSAGE.—

Intramuscular, Intravenous: Adults, 10 mg initially; if sedation is not severe, the subsequent dosage may be increased to 20 to 50 mg every two or three hours (maximal dose, 400 mg/day). *Children*, 5 mg/kg of body weight divided into four doses during a 24-hour period (maximal dose, 300 mg/day).

Oral: For motion sickness, *adults*, 50 mg one-half hour before departure and 50 mg before each meal; *children*, 5 mg/kg of body weight divided into four doses during a 24-hour period (maximal dose, 300 mg/day).

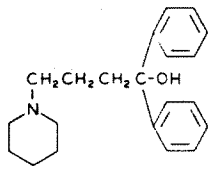
PREPARATIONS.—Benadryl (Parke, Davis).

Injection: Solution 10 mg/ml in 10 and 30 ml containers, 50 mg/ml in 1 and 10 ml containers.

Oral: Capsules 25 and 50 mg; elixir 12.5 mg/5 ml.

ADDITIONAL TRADEMARKS.—Bax (McKesson), Hista-Sed (Century), Niramine (Rachelle), Rohydra (Robinson). Drug also marketed by other manufacturers under generic name.

DIPHENIDOL [Vontrol]
DIPHENIDOL HYDROCHLORIDE [Vontrol Hydrochloride]



Diphenidol is useful in the management of nausea and vomiting associated with infectious diseases, malignancies, radiation sickness, general anesthesia, and treatment with antineoplastic agents. In adults, this drug also is effective in the management of vertigo in motion sickness, labyrinthitis following surgery of the middle and inner ear, and Meniere's disease. Its use in the treatment of vertigo in children has not been investigated.

Patients who are receiving diphenidol should be closely supervised, and therapy should be discontinued if auditory and visual hallucinations, disorientation, and confusion occur. Even then, the benefits of using this agent should outweigh the possible risks. The drug occasionally has produced drowsiness, dryness of the mouth, and dizziness. Effects reported rarely include rash, heartburn, headache, nausea, indigestion, blurred vision, malaise, and mild transient hypotension.

USUAL DOSAGE.—

Intramuscular: Adults, 20 to 40 mg four times daily; *children*, 3 mg/kg of body weight daily divided into four doses. No dosage has been established for *infants weighing less than 12 kg.*

Intravenous: Adults, 20 mg initially; dose is repeated in one hour if necessary. No dosage has been established for *children* of any age.

Oral, Rectal: Adults, 25 to 50 mg four times daily; *children*, 5 mg/kg of body weight daily divided into four doses.

PREPARATIONS.—(All strengths expressed in terms of the base.)

Vontrol [base] (Smith Kline & French).

Rectal: Suppositories 25 and 50 mg.

Vontrol [hydrochloride] (Smith Kline & French).

Injection: Solution 20 mg/ml in 2 ml containers.

Oral: Tablets 25 mg.

HYDROXYZINE HYDROCHLORIDE [Atarax, Vistaril IM]
HYDROXYZINE PAMOATE [Vistaril Pamoate]

Hydroxyzine is promoted as an antianxiety agent, but it also possesses antiemetic and antihistaminic properties. It is useful for the prevention and treatment of postoperative nausea and vomiting and motion sickness. The duration of action of hydroxyzine is four to six hours. (Also see Chapter 28, Antianxiety Agents.)

The incidence of drowsiness is low.

USUAL DOSAGE.—

Hydroxyzine Hydrochloride:

Intramuscular: Preoperatively and postoperatively, *adults*, 25 to 100 mg; *children*, 1 mg/kg of body weight.

Hydroxyzine Hydrochloride, Hydroxyzine Pamoate:

Oral: For motion sickness, *adults*, 25 to 100 mg three or four times daily. *Children under 6 years of age*, 50 mg divided into four doses during a 24-hour period; *over 6 years*, 50 to 100 mg divided into four doses during a 24-hour period.

PREPARATIONS.—

Hydroxyzine Hydrochloride:

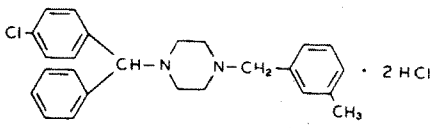
Atarax (Roerig). *Oral:* Syrup 10 mg/5 ml; tablets 10, 25, 50, and 100 mg.

Vistaril IM [hydrochloride] (Pfizer). *Injection:* Solution 25 mg/ml in 1 and 10 ml containers and 50 mg/ml in 1, 2, and 10 ml containers.

Hydroxyzine Pamoate:

Vistaril [pamoate] (Pfizer). *Oral:* Capsules 25, 50, and 100 mg; suspension 25 mg/5 ml.

MECLIZINE HYDROCHLORIDE [Antivert, Bonine]



Meclizine is effective in preventing and treating motion sickness. It has a slower onset and longer duration of action than most of the other antihistamines used for motion sickness; the duration of action of a single oral dose is 12 to 24 hours. Meclizine also is used in the treatment of nausea and vomiting associated with vertigo, labyrinthitis, Meniere's disease, and radiation sickness.

Drowsiness, blurred vision, dryness of the mouth, and fatigue have occurred following administration of meclizine. See the Introductory Statement for a discussion on the drug's possible teratogenic effects when used during pregnancy.

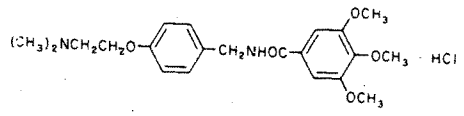
USUAL DOSAGE.—*Oral: Adults*, for motion sickness, 25 to 50 mg once daily. The initial dose should be taken at least one hour prior to departure. For other conditions, 25 to 100 mg daily. *Children*, dosage has not been established.

PREPARATIONS.—

Antivert (Roerig). *Oral:* Tablets 12.5 mg; tablets (chewable) 25 mg.

Bonine (Roerig). *Oral:* Tablets (chewable) 25 mg.

TRIMETHOBENZAMIDE HYDROCHLORIDE [Tigan]



This drug may be useful in alleviating nausea and reducing the frequency of vomiting in the immediate postoperative period after use of a general or spinal anesthetic, as well as in the treatment of nausea and vomiting during pregnancy. Its duration of action is four to six hours. Trimethobenzamide is of little or no value in the prevention and treatment of motion sickness.

The incidence of adverse effects is low; however, drowsiness, vertigo, diarrhea, cutaneous hypersensitivity reactions, extrapyramidal reactions, exaggeration of pre-existing nausea, pain at the site of injection, and local irritation after rectal administration have been noted.

USUAL DOSAGE.—

Intramuscular: Adults, 200 mg three or four times daily. To prevent postoperative vomiting, a single dose of 200 mg may be given before or during surgery; this dose may be repeated three hours after termination of anesthesia if needed.

Oral : Adults, 250 mg three or four times daily; *children*, 15 mg/kg of body weight divided into three or four doses during a 24-hour period.

Rectal : Adults, 200 mg; *children*, 15 mg/kg of body weight divided into three or four doses during a 24-hour period. This route should not be used in *premature or newborn infants.*

PREPARATIONS.—Tigan (Roche).

Injection :Solution 100 mg/ml in 2 and 20 ml containers.

Oral :Capsules 100 and 250 mg.

Rectal : Suppositories 200 mg (with 2% benzocaine).

PHENOTHIAZINE ANTIEMETICS

CHLORPROMAZINE [Thorazine]
CHLORPROMAZINE HYDROCHLORIDE
[Thorazine Hydrochloride]

Chlorpromazine is the prototype of the phenothiazine compounds. In addition to its calming action, it is effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins. It is not useful in preventing motion sickness. Since chlorpromazine has a prolonged half-life, the timed-release preparation does not offer any significant advantage over the ordinary oral dosage form.

Some patients may become drowsy to an undesirable degree; however, tolerance to excessive sedation usually develops after continued use. Chlorpromazine prolongs postanesthesia sleeping time. Among its more serious untoward reactions, which occur after long-term administration or large doses, are extrapyramidal reactions, orthostatic hypotension, cholestatic jaundice, and leukopenia. Because of the severity of these reactions, the phenothiazines should be used only when vomiting cannot be controlled by less hazardous agents. (See also the Introductory Statement and Chapter 29, Antipsychotic Agents.)

USUAL DOSAGE.—

Intramuscular : Adults, 25 to 50 mg every three or four hours until vomiting stops; the drug is then given orally. *Children*, 0.5 mg/kg of body weight every four to six hours.

Oral : Adults, 10 to 25 mg every four to six hours; *children*, 0.5 mg/kg of body weight every four to six hours.

Rectal : Adults, 100 mg every six to eight hours; *children*, 1 mg/kg of body weight every six to eight hours.

PREPARATIONS.—

Thorazine [base] (Smith Kline & French). *Rectal* :Suppositories 25 and 100 mg.

Thorazine [hydrochloride] (Smith Kline & French).

Injection :Solution 25 mg/ml in 1, 2, and 10 ml containers.

Oral : Capsules (timed-release) 30, 75, 150, 200, and 300 mg; solution (concentrate) 30 and 100 mg/ml; syrup 10 mg/5 ml; tablets 10, 25, 50, 100, and 200 mg.

FLUPHENAZINE HYDROCHLORIDE
[Permitil, Prolixin]

Fluphenazine is effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins. However, it is not useful in preventing motion sickness. This phenothiazine has virtually no sedative effect and, when given preoperatively, does not appreciably prolong postanesthesia sleeping time. Since fluphenazine hydrochloride has a prolonged half-life, the oral timed-release preparation does not offer any significant advantage over the ordinary oral dosage forms.

The incidence of extrapyramidal reactions is higher with fluphenazine than with most other phenothiazine compounds. This drug has little tendency to produce hypotension; however, blurred vision, dryness of the mouth, and urinary retention have been reported. (See also the Introductory Statement and Chapter 29, Antipsychotic Agents.)

USUAL DOSAGE.—*Intramuscular, Oral : Adults*, 1 to 2 mg; *children*, dosage is reduced (see table, back cover).

PREPARATIONS.—

Permitil (Schering). *Oral* : Solution (concentrate) 5 mg/ml; tablets 0.25, 2.5, 5, and 10 mg; tablets (timed-release) 1 mg.

Prolixin (Squibb).

Oral : Elixir 2.5 mg/5 ml; tablets 1, 2.5, and 5 mg.

Injection : Solution 2.5 mg/ml in 10 ml containers.

PERPHENAZINE [Trilafon]

This phenothiazine compound is effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins, but is not useful in preventing motion sickness. Since perphenazine has a prolonged half-life, the timed-release preparation does not offer any significant advantage over the ordinary oral dosage forms.

Untoward effects include extrapyramidal reactions, blurred or double vision, nasal congestion, dryness of the mouth, salivation, headache, and, occasionally, drowsiness. (See also the Introductory Statement and Chapter 29, Antipsychotic Agents.)

USUAL DOSAGE.—

Intramuscular : Adults, 5 to 10 mg. *Children 12 years of age and older*, 2 mg; *under 12 years*,

dosage has not been determined.

Oral : Adults, 8 to 24 mg daily in divided doses. *Children 1 to 6 years of age*, 4 mg daily divided into three doses; *6 to 12 years*, 6 mg daily divided into three doses; *12 years and older*, 6 to 12 mg daily divided into three doses.

PREPARATIONS.—Trilafon (Schering).

Injection : Solution 5 mg/ml in 1 and 10 ml containers.

Oral : Solution (concentrate) 16 mg/5 ml; syrup 2 mg/5 ml; tablets 2, 4, 8, and 16 mg; tablets (timed-release) 8 mg.

PROCHLORPERAZINE [Compazine]
PROCHLORPERAZINE EDISYLATE
[Compazine Edisylate]
PROCHLORPERAZINE MALEATE
[Compazine Maleate]

Prochlorperazine is effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins, especially when minimal sedation is desired. It is not useful in preventing motion sickness. Since prochlorperazine has an intrinsically prolonged action, the timed-release preparation does not appear to offer any significant advantage over the ordinary oral dosage forms.

This piperazine phenothiazine frequently causes extrapyramidal reactions. Although these effects are most likely to occur when large doses are used, signs may appear abruptly in patients taking only moderate doses. Therefore, it is contraindicated in patients with a history of dyskinetic reactions or epilepsy or in pregnant women with pre-eclampsia. (See also the Introductory Statement and Chapter 29, Antipsychotic Agents.)

USUAL DOSAGE.—

Intramuscular (edisylate): *Adults*, 5 to 10 mg every three to four hours; amount should not exceed 40 mg daily. *Children weighing over 10 kg*, 0.2 mg/kg of body weight.

Oral (edisylate, maleate): *Adults*, 5 to 10 mg three or four times daily; *children weighing over 10 kg*, 0.4 mg/kg of body weight divided into three or four doses during a 24-hour period.

Rectal (base): *Adults*, 25 mg twice daily; *children weighing over 10 kg*, 0.4 mg/kg of body weight divided into three or four doses during a 24-hour period.

PREPARATIONS.—

Compazine [base] (Smith Kline & French). *Rectal:* Suppositories 2.5, 5, and 25 mg.

Compazine [edisylate] (Smith Kline & French). *Injection:* Solution 5 mg/ml in 2 and 10 ml containers.

Oral: Solution (concentrate) 10 mg/ml; syrup 5 mg/5 ml.

Compazine [maleate] (Smith Kline & French). *Oral:* Capsules (timed-released) 10, 15, 30, and 75 mg; tablets 5, 10, and 25 mg.

PROMAZINE HYDROCHLORIDE [Sparine]

Promazine is effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins. However, since the incidence of adverse reactions (eg, drowsiness, orthostatic hypotension) is greater with this phenothiazine than with other agents in this group, especially after parenteral administration, other antiemetics are preferred. (See also the Introductory Statement and Chapter 29, Antipsychotic Agents.)

USUAL DOSAGE.—There is no reason to use this drug as an antiemetic because equally effective but safer agents are available. The manufacturer's suggested dosage is: *Intramuscular, Intravenous, Oral: Adults*, 25 to 50 mg; dose may be repeated at four- to six-hour intervals. *Children*, dosage has not been established.

PREPARATIONS.—Sparine (Wyeth).

Injection: Solution 25 and 50 mg/ml in 1, 2 and 10 ml containers.

Oral: Solution (concentrate) 30 and 100 mg/ml; syrup 10 mg/5 ml; tablets 10, 25, 50, 100, and 200 mg.

PROMETHAZINE HYDROCHLORIDE
[Phenergan]

Unlike other phenothiazines, promethazine is effective in the prevention and treatment of motion sickness. Its sedative action is of value in the treatment of postoperative nausea and vomiting. Promethazine also exhibits pronounced antihistaminic activity. Results of controlled studies in individuals who were subjected to severe motion indicate that a synergistic effect occurs when 25 mg of promethazine is given with 10 mg of dextroamphetamine or 50 mg of ephedrine.

Promethazine is relatively free of the extrapyramidal stimulation that is associated with some other phenothiazine derivatives. However, the usual precautions recommended for drugs in this class should be observed.

See also the Introductory Statement; Chapter 20, Adjuncts to Anesthesia; and Chapter 45, Antihistamines.

USUAL DOSAGE.—*Intramuscular, Oral, Rectal: Adults,* 12.5 to 25 mg every four to six hours; *children over three months of age,* 0.25 to 0.5 mg/kg of body weight every four to six hours.

PREPARATIONS.—Phenergan (Wyeth).

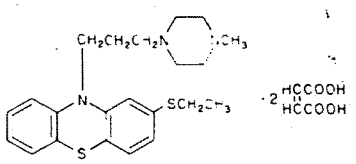
Injection: Solution 25 and 50 mg/ml in 1 and 10 ml containers.

Oral: Syrup 6.25 and 25 mg/5 ml; tablets 12.5, 25, and 50 mg.

Rectal: Suppositories 25 and 50 mg.

ADDITIONAL TRADEMARKS.—Fellozine (Fellows-Testagar), Ganphen (Tutag).

THIETHYLPERAZINE MALEATE [Torecan Maleate]



Thiethylperazine is useful in reducing the incidence of nausea and vomiting associated with vertigo and with the administration of general anesthetics, nitrogen mustards, and ionizing radiation. This phenothiazine is not useful in preventing motion sickness and may be ineffective when vomiting is caused by emotional disturbances.

Untoward effects occur infrequently and are mild and transitory with usual doses. Adverse reactions noted occasionally include drowsiness, dizziness, dryness of the mouth and nose, tachycardia, and anorexia. Moderate hypotension also has occurred occasionally within 30 minutes after administration of the drug to patients recovering from general anesthesia. Like other phenothiazine compounds, thiethylperazine may produce extrapyramidal stimulation. Symptoms may appear even after a single dose and abate if therapy is discontinued. (See also the Introductory Statement.)

USUAL DOSAGE.—*Intramuscular, Oral, Rectal: Adults,* 10 to 30 mg daily.

PREPARATIONS.—Torecan Maleate (Sandoz).

Injection: Solution 5 mg/ml in 2 ml containers.

Oral: Tablets 10 mg.

Rectal: Suppositories 10 mg.

TRIFLUPROMAZINE HYDROCHLORIDE [Vesprin]

This phenothiazine compound is effective in the management of postoperative nausea and vomiting, radiation sickness, and nausea and vomiting due to toxins. It is not useful in preventing motion sickness.

Trifluprom azine produces less sedation than some other phenothiazines (eg, promazine), but it prolongs the postanesthesia sleeping time. Extrapyramidal reactions have been observed following even single doses of this compound. (See also the Introductory Statement and Chapter 29, Antipsychotic Agents.)

USUAL DOSAGE.—

Intramuscular: Adults, 5 to 10 mg, repeated in four hours if necessary; *children,* 1 mg for each year of age (maximum, 10 mg daily).

Intravenous: Adults, 1 to 3 mg, repeated in four hours if necessary; *children 7 to 14 years of age,* 2 to 3 mg; *under 7 years,* 1 to 2 mg.

Oral: Adults, 20 to 30 mg daily; *children,* 1 mg for each year of age (maximum, 10 mg daily).

PREPARATIONS.—Vesprin (Squibb).

Injection: Solution 10 mg/ml in 10 ml containers, 20 mg/ml in 1 ml containers.

Oral: Suspension 50 mg/5 ml; tablets 10, 25, and 50 mg.

MIXTURES

Fixed-ratio combinations containing nonphenothiazine antiemetics and other ingredients (eg, pyridoxine, niacin, pentobarbital) are marketed, but there are no controlled studies to support the contention that these combinations, particularly those containing pyridoxine, have any advantage over the nonphenothiazine agent alone; therefore, single-entity preparations are preferred.

Anti-Nausea Supprettes (Webster): Each suppository contains pyrilamine maleate 25 or 50 mg and pentobarbital sodium 30, 45, or 100 mg.

Bendectin (Merrell-National): Each tablet contains dicyclomine hydrochloride 10 mg, doxylamine succinate 10 mg, and pyridoxine hydrochloride 10 mg.

Bucladin (Stuart): Each tablet contains buclizine hydrochloride 50 mg, pyridoxine hydrochloride 10 mg, scopolamine hydrobromide 0.2 mg, hyoscyamine sulfate 0.05 mg, and atropine sulfate 0.05 mg.

Cerebel Liquid (Xttrium): Each 5 ml contains

scopolamine hydrobromide 0.003 mg, phenobarbital 2.02 ml, milk of bismuth 2.5 ml, cerium oxalate 300 mg, hyoscyamine sulfate 0.0052 mg, and atropine sulfate 0.01 mg.

Delkadon (Merck Sharp & Dohme): Each tablet contains scopolamine hydrobromide 0.006 mg, hyoscyamine hydrobromide 0.225 mg, atropine sulfate 0.019 mg, and vinbarbital 30 mg.

Dramamine-D (Searle): Each tablet contains dimenhydrinate 50 mg and dextroamphetamine sulfate 5 mg.

Emesert (Arnar-Stone): Each suppository contains pyrilamine maleate 25 or 50 mg and pentobarbital 30, 45, or 100 mg.

Hytrona (Webster): Each tablet and 5 ml of elixir contains scopolamine hydrobromide 0.005 mg, hyoscyamine hydrobromide 0.180 mg, atropine sulfate 0.015 mg, and phenobarbital 16 mg.

Pyretol (First Texas): Each 5 ml of elixir contains scopolamine hydrobromide 0.0081 mg, chlorpheniramine maleate 2 mg, hyoscyamine sulfate 0.1296 mg, atropine sulfate 0.0242 mg, thiamine mononitrate 12.5 mg, and pyridoxine hydrochloride 25 mg.

Chapter 78

ANTISPASMODICS

Antispasmodics are used primarily to reduce the frequency and force of gastrointestinal smooth muscle contractions which, when excessive, often cause intense pain. Although smooth muscle spasm can be relieved by drugs that act at a number of different sites, those most commonly used are anticholinergic agents which act wholly or partly by blocking the action of acetylcholine at postganglionic parasympathetic sites.

Various parasympathetically innervated organs demonstrate different sensitivities to anticholinergic drugs, depending upon the dose. Small doses inhibit the production of saliva, sweat, and bronchial secretions. Slightly larger doses reduce parasympathetic input to the heart and eye; this causes tachycardia, loss of visual accommodation, and mydriasis. Moderate doses block the actions of cholinergic nerves supplying the bladder and gut so that urination is impeded and peristalsis is reduced. Still larger doses diminish gastric secretion. Because of the nonspecificity of these anticholinergic actions, an effective antispasmodic and antisecretory dose of any of these drugs also may be expected to produce side effects (eg, dryness of the mouth, blurred vision, constipation, dysuria).

Anticholinergic antispasmodics, which include the naturally occurring belladonna alkaloids, their derivatives, and numerous synthetic substitutes, are frequently used as adjuncts in the management of peptic ulcer. When adequate doses are administered, these drugs effectively relieve pain by inhibiting motility; their antisecretory effects also may contribute to relief of pain. However, there is no conclusive evidence that they facilitate healing of the ulcer or prevent complications or recurrences. Antispasmodics also are used as adjuncts in the treatment of functional bowel disorders (eg, irritable colon), mild dysentery, diverticulitis, and pancreatitis. They are of little or no value in pylorospasm, diaphragmatic hernia, asymptomatic diverticulosis, biliary dyskinesia, and dysmenorrhea. Opinion is divided on their usefulness in regional enteritis and ulcerative colitis.

Antispasmodics are generally administered orally before meals and at bedtime; long-acting and timed-release preparations are given less frequently. Some antispasmodics may be used parenterally to treat acute symptoms.

Belladonna Drugs: These drugs are available as the naturally occurring alkaloids of belladonna, as the individual active agents, as mixtures of the individual alkaloids, and as quaternary ammonium derivatives of the alkaloids. The naturally occurring anticholinergic alkaloids of belladonna are hyoscyamine and scopolamine (hyoscine). Hyoscyamine, the main active alkaloid, racemizes to atropine on extraction but its antimuscarinic activity is due primarily to the *l*-isomer. There are no qualitative differences in the antimuscarinic effects of atropine and scopolamine. Atropine, the prototype of this group, antagonizes the effect of acetylcholine at peripheral neuroeffector sites. It does not block transmission at the neuromuscular junction of skeletal muscle and has no effect on transmission at autonomic ganglia except when administered in toxic doses. It is readily absorbed from the gastrointestinal tract and readily crosses the blood-brain barrier, where large doses stimulate (presumably by leaving the adrenergic system unopposed) and toxic doses depress the central nervous system.

Atropine reduces both the motility and secretory activity of the gastrointestinal system. It reduces the tone of the ureter and urinary bladder and has a slight relaxant action on the bile ducts and gallbladder. It has little effect on

the myometrium. Atropine antagonizes the effects of cholinergic drugs on the gastrointestinal system, but is less effective in counteracting the action of these drugs on the urinary bladder.

Synthetic Anticholinergic Agents: The synthetic anticholinergic agents (see Table 1) are quaternary ammonium compounds, with the exception of oxyphencyclimine [Daricon, Vio-Thene], which is a tertiary amine; thus the latter's actions are similar to those of atropine. The natural alkaloids of belladonna are also tertiary amines, but several quaternary ammonium derivatives are also available. The quaternary ammonium compounds differ from atropine in several important respects: (1) They are less readily absorbed when given orally and there is considerable individual variability in response. (2) They rarely exert an effect on the central nervous system because they do not readily cross the blood-brain barrier. (3) Their duration of action is longer than that of the belladonna alkaloids. (4) In addition to their antimuscarinic effects, these drugs may interfere with transmission in autonomic ganglia, an action that both contributes to the therapeutic effect and may cause such reactions as orthostatic hypotension and impotence. (5) At toxic dose levels they can produce neuromuscular blockade which, in turn, may cause respiratory arrest. Some differences exist in the ratios of ganglionic blocking effect to antimuscarinic effect. However, most of the pharmacologic action of the drugs at usual doses is attributed to the antimuscarinic effect.

There appears to be little clinical evidence that certain quaternary ammonium compounds have selective anticholinergic actions. Clinically effective doses always evoke adverse effects, and such doses may exceed those usually recommended by manufacturers.

Other Synthetic Antispasmodics: A number of synthetic antispasmodics (see Table 2) relax smooth muscle primarily by exerting a nonspecific direct action on muscle fiber. These agents have little or no antimuscarinic activity and exert little effect on gastric secretion; they are most useful in the treatment of gastrointestinal disorders characterized by hypermotility and spasm.

Adverse Reactions and Precautions

Most untoward effects associated with the use of anticholinergic agents are manifestations of their pharmacologic actions: dryness of the mouth, anhidrosis, mydriasis, cycloplegia, tachycardia, constipation, and dysuria may be expected to appear after administration of full therapeutic doses of these drugs. Dermatologic reactions also may occur. Tolerance develops to many of these adverse reactions with prolonged administration, but this may be accompanied by a decrease in therapeutic effectiveness. Toxic doses may produce extreme dryness of the mouth accompanied by a burning sensation, dysphagia, thirst, marked photophobia, flushing of the skin, fever, leukocytosis, rash, nausea, vomiting, and hypertension.

Large doses of the belladonna drugs or other nonquaternary agents may produce signs of central nervous system stimulation (eg, restlessness, tremor, irritability, delirium, hallucinations). Stimulation may be followed by depression and death from medullary paralysis. Children are more susceptible to the toxic effects of these drugs than adults.

Large doses of the quaternary ammonium compounds may cause ganglionic blockade, as evidenced by orthostatic hypotension and impotence, and toxic doses may cause respiratory arrest as a result of neuromuscular blockade. Since quaternary ammonium compounds do not readily cross the blood-brain barrier, central nervous system effects occur only rarely.

Anticholinergic antispasmodics should be used with caution in patients with prostatic hypertrophy, pyloric obstruction, obstruction of the bladder neck, and cardiospasm. Because of their mydriatic effect, the anticholinergic drugs may precipitate an attack of acute glaucoma in patients predisposed to angle-closure. This has occurred occasionally after parenteral administration of these agents but has been reported only rarely after oral use. Anticholinergic drugs can be given safely to patients with open-angle glaucoma who are being treated with miotics. Antacids may interfere with absorption and should not be given simultaneously with anticholinergics.

Reactions observed with the other synthetic antispasmodics in this group are related to their direct action on smooth muscle or, occasionally, to hypersensitivity. Untoward effects reported with some of these drugs include drowsiness, euphoria, dizziness, asthenia, headache, nausea, constipation, diarrhea, hypotension, and rash.

BELLADONNA DRUGS

BELLADONNA EXTRACT

BELLADONNA LEAF
BELLADONNA LEAF FLUIDEXTRACT
BELLADONNA TINCTURE

For actions, indications, and adverse reactions, see the Introductory Statement.

USUAL DOSAGE.—

Belladonna Extract. *Oral: Adults*, 15 mg.

Belladonna Leaf. *Oral: Adults*, 30 to 200 mg.

Belladonna Leaf Fluidextract. *Oral: Adults*, 0.06 ml.

Belladonna Tincture. *Oral: Adults*, 0.6 ml three times daily; *children*, 0.1 ml/kg daily in three or four divided doses.

PREPARATIONS.—

Belladonna Extract, N.F. *Oral:* Tablets 15 mg.

Belladonna Leaf, U.S.P. and Belladonna Leaf Fluidextract, N.F. No single-entity pharmaceutical dosage forms available; compounding necessary for prescription.

Belladonna Tincture, U.S.P. *Oral:* Tincture in 4 oz, pint, and gallon containers.

All forms marketed under generic name.

Mixtures of Belladonna Alkaloids

BELLAFOLINE
DONNA
PRYDON

For actions, indications, and adverse reactions, see the Introductory Statement.

USUAL DOSAGE.—

Bellafoline (total levorotatory alkaloids of belladonna as maleates).

Oral: Adults, 1 or 2 tablets every four to six hours; *children*, 1/2 to 1 tablet every four to six hours.

Subcutaneous: Adults, 0.5 to 1 ml once or twice daily.

Donna. *Oral: Adults*, 1 tablet every 10 to 12 hours.

Prydon. *Oral: Adults*, 1 tablet every 12 hours.

PREPARATIONS.—

Bellafoline (Sandoz).

Oral: Tablets 0.25 mg.

Injection: Solution 0.5 mg/ml in 1 ml containers.

Donna (Robins). *Oral:* Each timed-release tablet contains hyoscyamine sulfate 0.311 mg, atropine sulfate 0.0582 mg, and scopolamine hydrobromide 0.0195 mg.

Prydon (Smith Kline & French). *Oral:* Each timed-release tablet contains belladonna alkaloids 0.4 or 0.8 mg, hyoscyamine sulfate 0.305 mg, atropine sulfate 0.060 mg, and scopolamine hydrobromide 0.35 mg.

MIXTURES

Many widely promoted mixtures contain antispasmodics in combination with other drugs such as barbiturates, antianxiety agents, and phenothiazines, or with antacids. If compatible agents are present in one dosage form in a ratio that satisfies the needs of an individual, use of the preparation may be convenient. However, these fixed-ratio products present certain problems.

Antispasmodics require greater individualization of dosage than most drugs. If the necessary adjustment of dosage of one component of a combination is made, the patient receives an inappropriate dosage of the other component since the dosage adjustments of the ingredients seldom parallel each other.

While sedatives may be appropriate for relieving the anxiety that is a component of many gastrointestinal disorders, a phenothiazine would rarely be the correct choice, because phenothiazines are primarily *antipsychotic* agents. Some antacids (eg, aluminum hydroxide) and charcoal present in other mixtures may interfere with the absorption of the antispasmodics.

For these reasons, the routine use of these mixtures is not advisable; they are listed only to provide information.

Antrenyl-Phenobarbital (Ciba): Each tablet contains oxyphenonium bromide 5 mg and phenobarbital 15 mg.

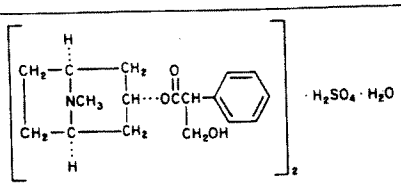
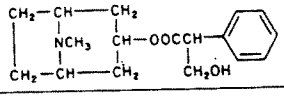
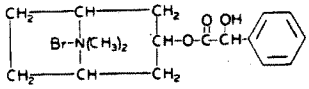
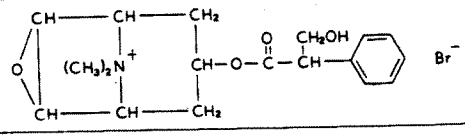
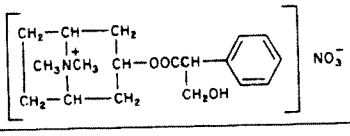
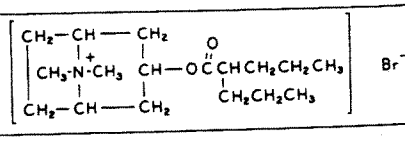
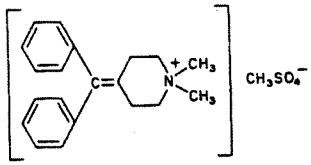
Banthine W/Phenobarbital (Searle): Each tablet contains methantheline bromide 50 mg and phenobarbital 15 mg.

Barbidonna (Mallinckrodt): Each tablet or 3.7 ml of elixir contains hyoscyamine sulfate 0.1286 mg, atropine sulfate 0.025 mg, scopolamine hydrobromide 0.0074 mg, and phenobarbital 16.2 mg; each No. 2 tablet contains hyoscyamine sulfate 0.1286 mg, atropine sulfate 0.025 mg, scopolamine hydrobromide 0.0074 mg, and phenobarbital 32.4 mg.

Bar-Don (Warren-Teed): Each tablet or 5 ml of elixir contains hyoscyamine hydrobromide 0.1 mg, scopolamine hydrobromide 0.007 mg, atropine sulfate 0.02 mg, and phenobarbital 16.67 mg.

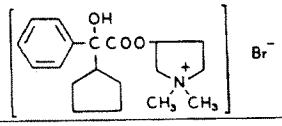
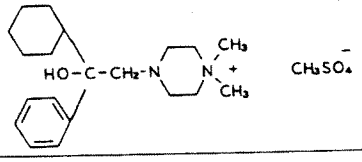
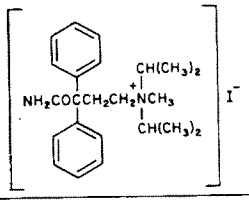
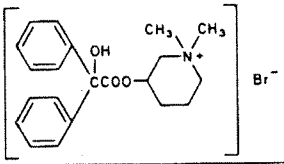
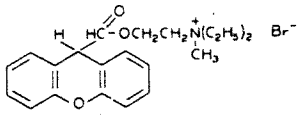
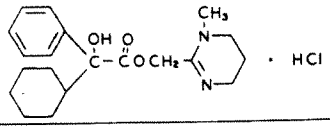
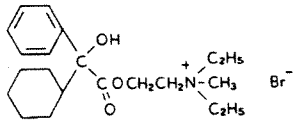
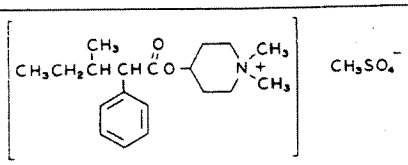
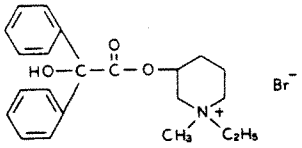
Belap (Lemmon): Each tablet contains belladonna extract 8.1 mg; and phenobarbital 8.1, 16.2, or 32.4 mg; each timed-release tablet contains homatropine methylbromide 7.5 mg and amobarbital 50 mg.

TABLE 1—ANTICHOLINERGIC ANTISPASMODICS

Drug	Chemical Structure
Belladonna Alkaloids:	
Atropine Sulfate, U.S.P.	
Hyoscyamine Cystospaz (Alcon)	
Hyoscyamine Hydrobromide, N.F.	
Hyoscyamine Sulfate, N.F. Levsin (Kremers-Urban)	
Quaternary Ammonium Derivatives of Belladonna Alkaloids:	
Homatropine Methylbromide Homapin (Mission) Malcotran (Pennwalt) Mesopin (Endo) Novatrin (Ayerst) Drug also marketed under generic name.	
Methscopolamine Bromide Pamine Bromide (Upjohn) Drug also marketed under the name Scopolamine Methylbromide.	
Methylatropine Nitrate Metropine (Pennwalt) Drug also marketed under the name Atropine Methylnitrate.	
Synthetic Substitutes:	
Anisotropine Methylbromide Valpin (Endo)	
Diphemanil Methylsulfate Prantal Methylsulfate (Schering)	

Usual Dosage	Preparations
Oral: Adults, 0.3 to 1.2 mg every 4 to 6 hours. *Subcutaneous: Adults,* 0.5 mg every 4 to 6 hours. *Children,* 0.01 mg/kg every 4 to 6 hours.	Tablets 0.3, 0.4, and 0.6 mg Solution (for injection) 0.3, 0.4, 0.5, 0.6 and 1.2 mg/ml in 1, 20, and 30 ml containers Tablets (hypodermic) 0.3, 0.4, and 0.6 mg
Oral: Adults, 0.25 to 0.5 mg 3 times daily. *Children,* 0.125 to 0.25 mg 3 times daily.	Tablets 0.15 mg
Oral, Intramsucular, Subcutaneous, Intravenous: Adults, 0.25 mg every 4 to 6 hours.	No single-entity pharmaceutical dosage form available; compounding necessary for prescription
Oral: Adults, 0.125 to 0.25 mg every 4 to 6 hours. *Children 2 to 10 years,* one-half above dosage range; *children under 2 years,* one-fourth above dosage range. *Intramuscular, Subcutaneous, Intravenous: Adults,* 0.25 to 0.5 mg every 6 hours. When symptoms are controlled, oral medication is substituted. *Children,* dosage not established.	Elixir 0.125 mg/5 ml Tablets 0.125 and 0.25 mg Tablets (timed-release [Levsinex]) 0.375 mg Solution (for injection) 0.25 mg/ml in 1, 10, and 30 ml containers
Oral: Adults, 2.5 to 10 mg 4 times daily. *Children,* 3 to 6 mg 4 times daily (chewable tablets). *Infants,* for colic, 1 mg 4 times daily (elixir).	Homapin: Tablets 5 and 10 mg Malcotran: Tablets 10 mg Mesopin: Elixir 5 mg/5 ml; tablets 5 mg Novatrin: Tablets 5 mg
Oral: Adults, 2.5 to 5 mg 4 times daily. *Children,* 0.2 mg/kg daily in 4 doses. *Intramuscular, Subcutaneous: Adults,* 0.25 to 1 mg every 6 to 8 hours until acute symptoms are controlled and patient can take oral medication. *Children,* dosage not established.	Tablets 2.5 mg Solution (for injection) 1 mg/ml in 1 ml containers
Oral: Adults, 1 to 2 mg every 4 to 6 hours. *Infants and children under 5 years,* 0.25 to 0.5 mg every 3 hours. *Children over 5 years,* 0.5 to 1 mg every 3 hours.	Tablets 1 mg
Oral: Adults, 10 mg 3 or 4 times daily. *Children* dosage not established.	Elixir 10 mg/5 ml Tablets 10 mg
Oral: Adults, initially, 100 mg every 4 to 6 hours; maintenance dose 50 to 100 mg every 4 to 6 hours; timed-release preparation, 100 or 200 mg every 8 hours. *Children,* dosage not established.	Tablets 100 mg Tablets (timed-release) 100 mg

TABLE 1—ANTICHOLINERGIC ANTISPASMODICS (Cont'd.)

Drug	Chemical Structure
Glycopyrrolate Robinul (Robins)	
Hexocyclium Methylsulfate Tral (Abbott	
Isopropamide Iodide Darbid (Smith Kline & French)	
Mepenzolate Bromide Cantil (Lakeside)	
Methantheline Bromide Banthine (Searle)	
Oxyphencyclimine Hydrochloride* Daricon (Beecham-Massengill) Vio-Thene (Rowell	
Oxyphenonium Bromide Antrenyl Bromide (Ciba)	
Pentapiperium Methylsulfate Quilene (Warner-Chilcott)	
Pipenzolate Bromide Piptal (Lakeside)	

*Tertiary amine. All others are quaternary ammonium compounds.

Therapeutic Approach to Ulcer Healing

ANDRE L. BLUM, M.D.
Zurich, Switzerland

The healing rate of duodenal ulcers may be accelerated by secretory inhibitors such as histamine H_2-receptor antagonists and pirenzepine, by antacids, by protective drugs such as sucralfate and colloidal bismuth, and by antidepressant drugs such as trimipramine. The effect of these drugs on the rate of healing is comparable; they differ with respect to practicability of treatment, incidence and types of side effects, and suitability for long-term administration. Currently, the most versatile and most thoroughly investigated drugs are the histamine H_2-receptor antagonists.

Accelerating the rate of ulcer healing is one of the six aims of ulcer treatment (**Table I**) [1]. It is often mentioned because it is easy to study, although from a clinical standpoint, it is the least important aim. During the last five years, over 300 articles on the effect of different drugs on the healing of duodenal ulcers have been published [2,3], and the ability to accelerate the rate of duodenal ulcer healing is often taken as a measure of the effectiveness of a drug. To evaluate the efficacy of an ulcer drug, however, the checklist shown in **Table II** should be used. It is up to the individual physician either to give equal importance to all 10 points, or to give more weight to certain points, such as improvement of ulcer pain and prevention of complications and recurrences, and less weight to other points, such as acceleration of the rate of ulcer healing.

DRUGS SUITED TO ACCELERATE HEALING OF DUODENAL ULCERS

Histamine H_2-Receptor Antagonists. The histamine H_2-receptor antagonists ranitidine and cimetidine inhibit acid secretion. The effect of a bedtime dose of ranitidine on nocturnal intragastric acidity is shown in **Figure 1**. When given at a dose of 150 mg twice daily, ranitidine inhibits acid secretion to a greater extent than does cimetidine at a dose of 1 g per day. A 300 mg dose of ranitidine at bedtime may be preferable to the "classical" two-dose regimen, at least for patients who smoke (**Table III**) [4]. In the case of cimetidine, a dose of 800 mg at bedtime is at least as effective as two 400 mg per day doses [5].

Figure 2 shows the results of eight studies in which ranitidine at a dose of 150 mg twice daily was compared with cimetidine at a dose of 1 g per day (200 mg three times per day with meals plus 400 mg at bedtime). On average, ranitidine had a 10 percent advantage over cimetidine, but this difference was statistically significant only in the study in which 794 patients were enrolled. It is estimated that at least 700 patients have to be studied to detect a difference of this magnitude.

An advantage of ranitidine over cimetidine is its lack of interaction with the metabolism of other drugs. Cimetidine inhibits the hepatic metabolism

From the Medizinische Klinik, Stadtspital Triemli, Zurich, Switzerland. This work was supported by Swiss National Foundation Grant 3.864.0.083. Requests for reprints should be addressed to Dr. Andre L. Blum, Medizinische Klinik, Stadtspital Triemli, CH-8063, Zurich, Switzerland.

of such drugs as diazepam, chlordiazepoxide, warfarin, phenindione, nicoumalone, phenytoin, carbamazepine, propranolol, labetalol, metoprolol, cholmethiazole, theophylline, and lignocaine [6]. Mental disturbances such as confusion and somnolence have been reported with cimetidine, mainly in the elderly, those with renal failure, and those receiving very large doses of the drug. No such effects have thus far been attributed to ranitidine. Cimetidine, but not ranitidine, has an anti-androgenic effect. Other side effects are rare with either drug [2,6].

It has been reported that relapse rates following initial ulcer healing are greater with cimetidine than with sucralfate [7] and with tripotassium dicitrato bismuthate [8], but this question has not yet been settled. The relapse rate was similar after cimetidine, antacids [9], trimipramine [10], and pirenzepine [11].

Antacids. Concentrated antacid gels with a buffering capacity of more than 7 meq/ml have a weak effect on intragastric pH (Figure 1). Standard antacid gels with a buffering capacity of 1 to 3 meq/ml have an almost negligible effect on intragastric pH. Despite this, antacids are quite effective in accelerating the rate of ulcer healing. As **Figure 3** shows, it is not even necessary to administer a large dose of an antacid to accelerate the rate of healing; small doses are at least as effective. In a study by Pace et al [12], an antacid gel with a neutralizing capacity of 120 meq per day had a similar effect on the healing of gastric ulcers as did 1 g of cimetidine per day. It has, therefore, been speculated that the favorable effect of antacids is not only mediated by a reduction in acidity, but also by the inactivation of bile acids, the stimulation of prostaglandin synthesis [13,14], or even the formation of a protective coating over the ulcer.

Sucralfate. This symposium issue deals extensively with sucralfate, which fulfills many of the conditions shown in Table II. The mechanism of action of sucralfate is not entirely clear; it is known that the drug forms a protective coating over the ulcer. In addition, it may inactivate pepsin and, to a certain degree, acid, bind bile salts, stimulate prostaglandin synthesis, and lead to morphologic alterations within the gastric mucosa (see articles by Tarnawski et al and Samloff in this symposium issue).

A disadvantage of sucralfate has been its relatively complicated intake schedule. It is noteworthy that sucral-

TABLE I Aims of Ulcer Treatment

- Accelerate healing rate of ulcer
- Reduce ulcer pain
- Prevent complications
- Prevent recurrences of ulcer
- Avoid side effects of treatment
- Reduce costs of treatment

TABLE II Characteristics of a Good Drug for Treating Ulcers

- Accelerates healing rate of ulcer
- Reduces pain of ulcer
- Prevents complications
- Results in a low relapse rate when discontinued after ulcer has healed
- Prevents recurrences when given on a long-term basis after ulcer has healed
- Produces no side effects
- Is based on a good scientific program; its mechanism of action is known
- Facilitates patient compliance; its mode and schedule of intake should be simple
- Is effective against both duodenal and gastric ulcers
- Is inexpensive

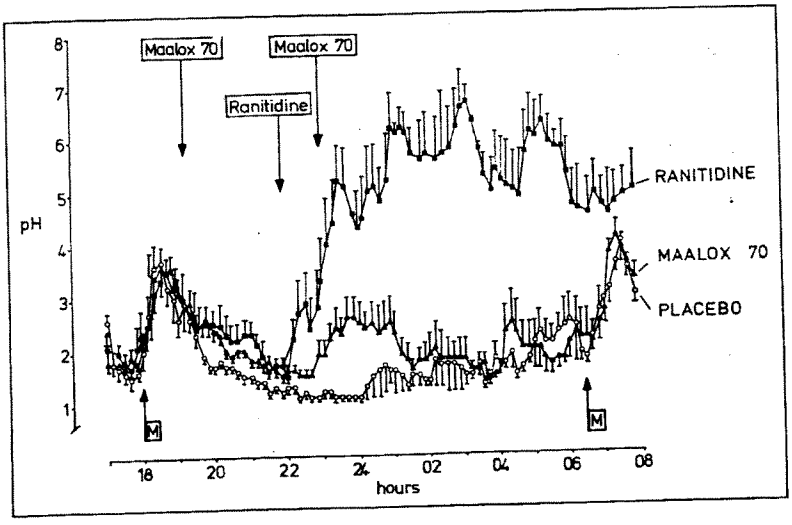


Figure 1. *Ambulatory intragastric pH of healthy volunteers given either placebo (n = 9), 10 ml lot, a concentrated antacid with a buffering capacity of 7 mEq/ml (n = 9), or a tablet of ranitidine (150 mg, n = 10). The mean pH with one SEM is shown for each 10-minute period (C. Fimmel, unpublished observation).*

TABLE III Comparison of Two Regimens of Ranitidine on Healing Rate of Duodenal Ulcers after Four Weeks

	150 mg Twice Daily Number (Percent)	300 mg at Bedtime Number (Percent)
Smokers	24/31 (75)	26/27 (96)
Nonsmokers	23/25 (96)	17/18 (94)

The difference in healing rates between the two regimens was statistically significant in patients who smoked.

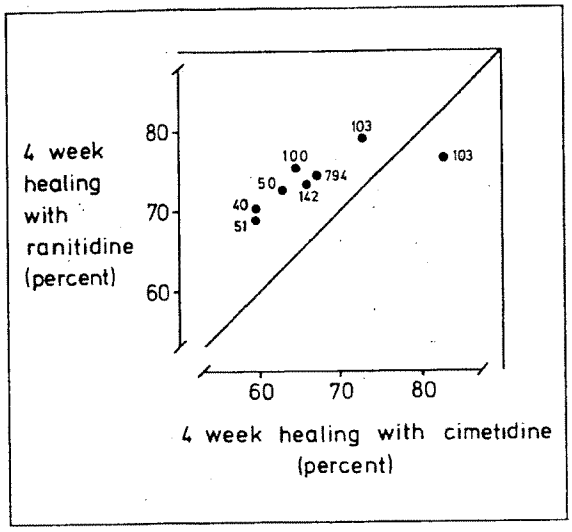


Figure 2. Comparison of four-week healing rates of duodenal ulcers with ranitidine (150 mg twice daily) and cimetidine (1 g per day) in 794 [49], 142 [50], 103 [51], 103 [52], 100 [53], 51 [54], 50 [55], and 40 patients [56], respectively. The difference in healing rates between ranitidine and cimetidine was statistically significant only in [49].

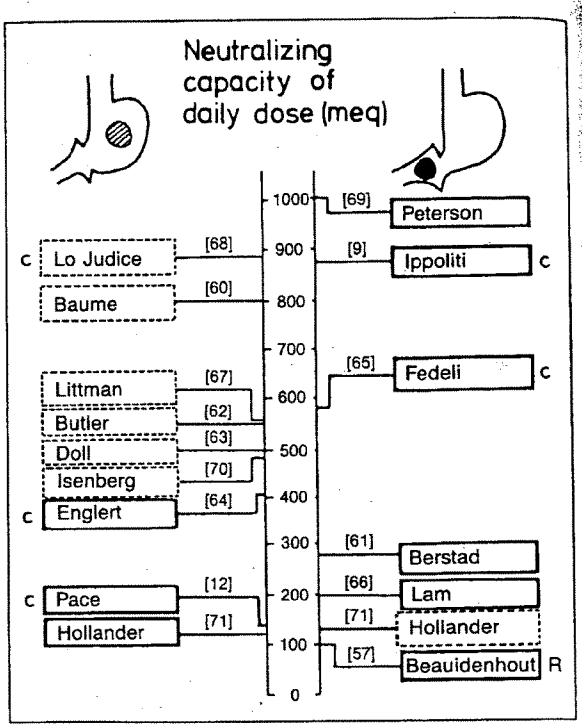


Figure 3. Healing of duodenal ulcer (right side) and gastric ulcer (left side) in antacid trials. The neutralizing capacity of one daily dose of the antacid is shown in the middle column. Solid rectangles represent trials in which the antacid was more effective than placebo. Rectangles with solid lines plus a C or R indicate trials in which antacids were equal in efficacy to cimetidine or ranitidine, respectively. Rectangles with interrupted lines represent trials in which antacids were no more effective than placebo and rectangles with interrupted lines and a C indicate trials in which antacids were inferior to cimetidine.

fate at a dose of 2 g twice daily is reported to be as effective as 1 g four times per day in the short-term treatment of duodenal ulcers (see article by Brandstaetter and Kratochvil in this symposium issue).

Colloidal Bismuth Compounds. Most studies showing a favorable effect of colloidal bismuth compounds on the rate of ulcer healing were performed with a suspension [15]. Many patients refuse to ingest this suspension because of its strong ammonia smell. Recently, bismuth tablets have been introduced with encouraging results [16–18].

Bismuth encephalopathy has never been observed with colloidal bismuth preparations. Drawbacks to treatment with bismuth compounds are the frequency with which they must be taken and a darkening of the feces, the tongue and, occasionally, the teeth.

Pirenzepine. Pirenzepine is an anticholinergic drug that inhibits muscarinic M1 effects (including gastric secretion) at doses lower than those required to block muscarinic M2 effects. The four-week healing rate of duodenal ulcers with 100 mg of pirenzepine per day is similar to that seen with 1 g of cimetidine per day [19–22]. Pirenzepine at a dose of 100 mg per day produces undesirable anticholinergic side effects in 5 to 10 percent of the patients treated.

Antidepressant Drugs. Trimipramine, a combination of imipramine, a tricyclic antidepressant, and levometromazin, accelerates duodenal ulcer healing. The drug is, however, inferior to cimetidine with respect to the rate of healing and the reduction in symptoms [23]. In addition, patients receiving trimipramine frequently complain of fatigue.

Experimental Drugs. Several prostaglandin analogues

have recently been tested. In one study, misoprostol was found to be inferior to cimetidine, with respect to both the rate of ulcer healing and the relief of ulcer symptoms [24].

New histamine H_2-receptor antagonists such as famotidine [25] might, on a molecular basis, inhibit acid secretion to a greater extent than ranitidine. In clinical use, however, no advantage of these agents over ranitidine has been demonstrated yet.

Omeprazole, a substituted benzimidazole, accelerates the rate of ulcer healing to a greater extent than does any other drug (E. Carlsson, AB Haessle, personal communication). The drug was withdrawn from clinical testing because it produced marked hypergastrinemia and hyperplasia of enterochromaffin-like cells of the gastric mucosa in the rat. The lesions resembled carcinoid tumors. Hypergastrinemia is the probable cause of the hyperplasia. Trials of omeprazole were resumed by some countries in early 1985.

PRACTICAL TREATMENT OF DUODENAL ULCERS

Drug Choice. All drugs mentioned previously can be used to treat duodenal ulcers; the best drug is the one which the prescribing physician is most familiar with. Smoking slows healing, particularly in patients not treated with an active drug [26]; other presenting characteristics such as age, sex, and acid secretion did not predict the outcome in two recently completed controlled clinical trials (Blum, unpublished observations). It would be desirable to use different types of drugs for different types of ulcers, but information to provide such selective medical treatment is unavailable. When ranitidine is used by patients who smoke, one dose of 300 mg at bedtime may be preferable to two daily 150 mg doses.

Length of Treatment. Treatment should be administered for four weeks. It has been claimed that it is sufficient to treat patients until their symptoms disappear, which would often be for less than four weeks. However, the time to symptomatic relapse in both duodenal and gastric ulcers is considerably shorter when healing is incomplete [27,28] and, therefore, I do not advocate this regimen. On the other hand, it is inadvisable to extend treatment with a curative dose beyond the time at which complete healing of the ulcer has been achieved [29].

Endoscopic Assessment. Symptoms either disappear before healing or persist after healing in about half of the patients with ulcers and, therefore, it makes little sense to use the disappearance of symptoms as an indication of healing. The advantage of assessing healing by endoscopy should be weighed against the disadvantage of yet another invasive and costly procedure for the patient.

Treatment Failures. Incomplete healing after four weeks is unsatisfactory and, after eight weeks, should be considered a failure of treatment. In these cases, treatment should be changed; simply continuing with the regimen used thus far is not recommended [30]. It is better to switch to another drug. For example, treatment failures with cimetidine have successfully been treated by colloidal bismuth tablets (**Table IV**) [31]. In one study, patients who had not responded to cimetidine responded well to ranitidine, although non-responders to ranitidine did not respond well to cimetidine [32]. Increasing the dosage of a previously used drug is less effective than switching regimens. Two studies showed that increasing the dose of cimetidine was unsatisfactory [31,33]. It is unknown whether adding another drug to the regimen in use is more effective than switching regimens. The combination of cimetidine plus sucralfate was no more effective than either one of these two drugs alone (see Van Deventer et al in this symposium issue). The combination of an anticholinergic drug plus an antacid plus cimetidine was as effective as the combination without cimetidine [34].

TABLE IV **Comparison of Tripotassium Dicitrato Bismuthate and High-Dose Cimetidine in Treating Duodenal Ulcers Resistant to Standard Dose of Cimetidine***

	Tripotassium Dicitrato Bismuthate	Cimetidine
	Four Tablets per Day	400 mg per Day
Number (percent)†	10/12 (83)	5/13 (39)

*Longest diameter of ulcer had decreased by less than 25 percent four weeks after treatment with 1 g of cimetidine per day.
†The difference in healing rates after four weeks between the two treatments was statistically significant.

Maintenance Therapy. Long-term maintenance therapy should be given to all patients in whom elective surgery is considered. These include patients who have had several painful ulcer attacks within a short time (at least two attacks during the last year); those who have bleeding; those who have concomitant disease in which ulcer recurrences should be avoided at all costs, such as patients receiving anticoagulants; and those who have a high risk of a recurrence, such as smokers. It is desirable to prescribe the same drug that led to healing of the ulcer but to decrease the dose. Ranitidine can be given in a 150 mg dose at bedtime, and cimetidine in a dose of 1 g twice daily. The relapse rate with long-term medical maintenance treatment is approximately 10 times higher than with proximal gastric vagotomy [35–37], but surgery can be avoided permanently in an estimated 50 percent of the patients receiving maintenance treatment. There is an ongoing discussion concerning whether long-term reduction of gastric acidity by secretory inhibitors promotes the development of gastric cancer [38]. To date, there is no evidence that it does, but the possibility cannot yet be dismissed. The same is true for gastric resection and vagotomy.

Maintenance treatment is best given on a continuous basis for at least one year. There are no upper limits to the

TABLE V Comparison of Ranitidine and Cimetidine in Preventing Recurrences after Healing of Duodenal Ulcers

		Percentage of Recurrences after One Year	
		Ranitidine	Cimetidine
Study	Number Enrolled	150 mg at Bedtime	400 mg at Bedtime
[42]*	99	12	30
[43]*	375	15	29
[58]	92	30	36
[59]	61	25	24

*The difference in recurrence rates between ranitidine and cimetidine was statistically significant.

duration of maintenance treatment [36]. A number of patients probably use maintenance treatment on demand, which means they simply take their drug for a few days or a few weeks when they start having symptoms. This probably works quite well, since the number of patients seen with ulcer attacks is decreasing in the outpatient departments of many hospitals, although the proportion of those with ulcers resistant to treatment is increasing. In controlled studies, a favorable effect of treatment on demand could not be proved [39,40]. Another possibility is to treat patients during the seasons when they usually have ulcer recurrences [41]. However, in most patients, ulcer recurrence does not follow a seasonal pattern.

Recurrences. Symptomatic recurrences occur within one year in approximately 20 percent of patients maintained with cimetidine; with ranitidine, recurrences may be less frequent (**Table V**) [42,43]. Since smoking may decrease the effect of a secretory inhibitor [44], patients who smoke should stop, although a beneficial effect of abstinence from smoking has never been shown conclusively [45]. The main reason for symptomatic recurrences during maintenance treatment is probably inadequate compliance and failure to take the drug regularly [46]. In patients with a symptomatic relapse, the recurrence can be treated by augmenting the dosage of a drug (for example, switching from 150 mg of ranitidine per day to 300 mg of ranitidine per day); treatment should be resumed after the ulcer has healed. Patients whose ulcers show resistance to a drug pose a major problem. It is not known whether switching to another drug helps in these cases. Moreover, it has been suggested that patients receiving secretory inhibitors who have a recurrence do not respond well to proximal gastric vagotomy [47], although these studies are inconclusive.

PRACTICAL TREATMENT OF GASTRIC ULCERS

Histamine antagonists, antacids, sucralfate, and colloidal bismuth preparations are helpful in treating gastric ulcers. Treatment of gastric ulcers differs from the treatment of duodenal ulcers in some respects. The healing rate of gastric ulcers is, on the average, slower than that of duodenal ulcers. The four-week healing rate is, on average, 50 percent. It is not easy, in an individual patient, to predict the response to treatment on the basis of presenting characteristics [48]. The only reliable predictor is ulcer size; large ulcers heal at a slower rate than do small ulcers. In the past, ulcers that still had not healed after 12 weeks of medical treatment were surgically treated. The main reason for this was the fear of overlooking gastric carcinoma. This is a highly unlikely occurrence today because it is now possible to obtain biopsy specimens during fiberendoscopy. Since partial gastric resection, which is still the most popular intervention for patients with gastric ulcers, has a mortality rate of approximately 2 percent the likelihood that a patient will die as a result of surgery is greater than the probability of death from an undetected malignancy. It is, however, mandatory to endoscopically assess gastric ulcers until they have healed completely.

Gastric ulcers reoccur, on average, at a lower rate than do duodenal ulcers [12]. Histamine H_2-receptor antagonists prevent relapses of gastric ulcers, but their effect is less marked with duodenal ulcers. In addition, the fear that long-term secretory inhibition in patients with gastric ulcers may promote the development of carcinoma cannot be completely rejected on the basis of present evidence [38].

REFERENCES

1. Blum AL: Ziele bei der Therapie der Ulkuskrankheit. Schweiz Med Wochenschr 1984; 114: 679–683.
2. Blum AL, Siewert JR, eds. Ulcus-Therapie. Interdisziplinaere Gastroenterologie, ed 2. Berlin: Springer-Verlag, 1982.
3. Isenberg JI, Johansson C, eds: Clinics in gastroenterology. Peptic ulcer disease. London: W.B. Saunders Company, 1984; 287–654.
4. Ireland A, Gear P, Colin-Jones DG, et al: Ranitidine 150 mg twice daily versus 300 mg nightly in treatment of duodenal ulcers. Lancet 1984; II: 274–278.
5. Delattre M, Dickson B: Cimetidine once daily (letter). Lancet 1984; I: 625.
6. Thomas JM, Misiewicz G: Histamine H_2-receptor antagonists in the short- and long-term treatment of duodenal ulcer. Clin Gastroenterol 1984; 13: 501–541.
7. Marks IN, Wright JP, Lucke W, Girdwood AH: Relapse rates following initial ulcer healing with sucralfate and cimetidine. Scand J Gastroenterol 1983; 18 (suppl 83): 53–56.
8. Martin DF, Hollanders D, May SJ, Ravenscroft MM, Tweedle DEF, Miller JP: Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. Lancet 1981; I: 7–10.

9. Ippoliti A, Elashoff J, Valenzuela J, Cano R, Frankl H, Samloff M, Koretz R: Recurrent ulcer after successful treatment with cimetidine or antacid. Gastroenterology 1983; 85: 875–880.
10. Berstad A, Aadand E, Bjerke K, Carlsen E: Relapse of duodenal ulcer after treatment with trimipramine/antacids or cimetidine/antacids. Scand J Gastroenterol 1981; 16: 933–936.
11. Eichenberger P, Giger M, Mattle W, et al: Treatment and relapse prophylaxis of duodenal ulcer with pirenzepine and cimetidine. Scand J Gastroenterol 1982; 17 (suppl 72): 197–206.
12. Pace F, Broker HJ, Caspary W, et al: Medikamentoese Therapie des ulcus ventriculi mit einem niedrig dosierten Antacidumgel und mit Cimetidin. DTW (in press).
13. Szelenyi I, Postius S, Engler H: Evidence for a functional cytoprotective effect produced by antacids in the rat stomach. Eur J Pharmacol 1983; 88: 403–406.
14. Tarnawski A, Hollander D, Cummings D, Krause WJ, Gergely H, Zipser RD: Are antacids acid neutralizers only? Histologic, ultrastructural, and functional changes in normal gastric mucosa induced by antacids (abstr). Gastroenterology 1984; 86: 1276.
15. Tytgat GN, Hameeteman W, Van Olffen GH: Sucralfate, bismuth compounds, substituted benzimidazoles, trimipramine, and pirenzepine in the short- and long-term treatment of duodenal ulcer. Clin Gastroenterol 1984; 13: 543–568.
16. Bianchi-Porro G, Petrillo M: An endoscopic controlled trial comparing De-Nol tablets and cimetidine tablets in the treatment of duodenal ulcer (abstr). Scand J Gastroenterol 1982; 17 (suppl 78): 99.
17. Tytgat GNJ, VanBentem N, VanOlffen G, Dekker W, Rutgerts L, DeBoer J: Controlled trial comparing colloidal bismuth subcitrate tablets, cimetidine, and placebo in the treatment of gastric ulceration. Scand J Gastroenterol 1982; 17 (suppl 80): 31–38.
18. Vantrappen G, Rutgeerts P, Broeckaert L, Janssens J: Randomized open controlled trial of colloidal bismuth subcitrate tablets and cimetidine in the treatment of duodenal ulcer. Gut 1980; 21: 329–333.
19. Brunner H: Pirenzepine and cimetidine in the treatment of peptic ulcer. Scand J Gastroenterol 1982; 17 (suppl 72): 207–209.
20. Giacosa A, Cheli R, Molinari F, Parodi MC: Comparison between ranitidine, cimetidine, pirenzepine, and placebo in the short-term treatment of duodenal ulcer. Scand J Gastroenterol 1982; 17 (suppl 72): 215–219.
21. Henry DA, Hawkey C, Sommerville K, et al: Pirenzepine and cimetidine in duodenal ulcer: a controlled trial. In: Dotevall G, ed. Advances in gastroenterology with the selective antimuscarinic compound pirenzepine. Amsterdam: Excerpta Medica, 1982; 214–216.
22. Galeone M, Cacioli D, Moise G, Gherardi G: Long-term management of duodenal ulcer with pirenzepine and cimetidine. A double-blind controlled clinical trial. Gazzetta Medica Italiana-Aggiornamenti Clinicoteraeutici 1980; 139: 691–694.
23. Becker U, Faurschou P, Jensen J, et al: Efficacy of trimipramine and cimetidine in the treatment of duodenal ulcer—a double-blind comparison. Scand J Gastroenterol 1983; 18: 137–143.
24. Aenishaenslin W, Schweiz. Ulcusstudiengruppe: Therapie des Ulcus duodeni mit einem Prostaglandin-Analogon: Misoprostol vs Cimetidin. Eine multizentrische Doppelblindstudie. Schweiz Med Wochenschr (in press).
25. Ryan R: Clinical pharmacology of famotidine: summary of data from the United States. Ital J Gastroenterol 1984; 16: 171–182.
26. Sonnenberg A, Muller-Lissner SA, Vogel E, et al: Predictors of duodenal ulcer healing and relapse. Gastroenterology 1981; 81: 1061–1067.
27. Miyake T, Ariyoshi J, Suzaki T, et al: Endoscopic evaluation of the effect of sucralfate therapy and other clinical parameters on the recurrence rate of gastric ulcers. Dig Dis Sci 1980; 25: 1–8.
28. Piper DW, Shinners J, Greig M, Thomas J, Woller SL: Effect of ulcer healing on the prognosis of chronic gastric ulcer: four-year follow-up. Gut 1978; 19: 419–424.
29. Bardhan KD, Cole DS, Hawkins BW, Franks C: Does treatment with cimetidine extended beyond initial healing of duodenal ulcer reduce the subsequent relapse rate? Br Med J 1982; 284: 621–623.
30. Bardhan KD: Cimetidine in duodenal ulcer: the present position. In: Torsoli A, Bucchelli PE, Brimblecombe RW, eds. Symposium on further experience with H_2-receptor antagonists in peptic ulcer disease and progress in histamine research. Amsterdam: Excerpta Medica, 1980; 5–14.
31. Lam SK, Lee NW, Koo J, Hui WM, Fok KH, Ng M: Randomized crossover trial of tripotassium dicitrato bismuthate versus high-dose cimetidine for duodenal ulcers resistant to standard dose of cimetidine. Gut 1984; 25: 706–730.
32. Mazzacca G, D'Agostino L, D'Arienzo A, et al: Cimetidine or ranitidine non-responder patients. Treatment of duodenal ulcers resistant to one H_2 blocker with the other (abstr). Scand J Gastroenterol 1982; 17 (suppl 78): 103.
33. Bardhan KD: Refractory duodenal ulcer. Gut 1984; 25: 711–717.
34. Adami HO, Bjorklund O, Enander LK, et al: Cimetidine or propantheline combined with antacid therapy for short-term treatment of duodenal ulcer. Dig Dis Sci 1982; 27: 388–393.
35. Andersen D, Amdrup E, Sorensen FH, Jensen KB: Surgery or cimetidine? II. Comparison of two plans of treatment: operation or cimetidine given as a low-dose maintenance dose. World J Surg 1983; 7: 378–384.
36. Gear MWL: Proximal gastric vagotomy versus long-term maintenance treatment with cimetidine for chronic duodenal ulcer. A prospective randomized trial. Br Med J 1983; 286: 98–99.
37. Gray GR, Smigh IS, McWhinnie D, Gillespie G: Five-year study of cimetidine or surgery for severe duodenal ulcer dyspepsia. Lancet 1982; I: 787–788.
38. Colin-Jones DG, Langman MJS, Lawson DH, Vessey MP: Cimetidine and gastric cancer: preliminary report from postmarketing surveillance study. Br Med J 1982; 285: 1311–1313.
39. Bardhan KD: Intermittent treatment of duodenal ulcer with cimetidine. Br Med J 1980; 81: 20–22.
40. Rune SJ, Mollman KM, Rahbek I: Frequency of relapses in duodenal ulcer patients treated with cimetidine during symptomatic periods. Scand J Gastroenterol 1980; 15 (suppl 58): 85–92.
41. Morelli A, Gaetani M, Pelli MA, et al: Prevention of duodenal ulcer relapse by seasonal treatment with pirenzepine. II: Results of a long-term follow-up in a double-blind trial (abstr). Gastroenterology 1983; 84: 1253.
42. Silvis SE: Ranitidine and cimetidine in long-term maintenance therapy for duodenal ulcer prevention: interim analysis of the multicentre study in the USA. In: Abstracts of the ranitidine therapeutic advances international symposium, Glaxo, London, March 1984.
43. Gough KR: Ranitidine and cimetidine in long-term maintenance therapy for duodenal ulcer prevention: interim analysis of the multicentre study in the United Kingdom, Eire, and Australia. In: Abstracts of the ranitidine therapeutic advances international symposium, Glaxo, London, March 1984.
44. Boyd EJS, Wilson JA, Wormsley KG: Smoking impairs therapeutic gastric inhibition. Lancet 1983; I: 95–97.
45. Doll R, Jones AF, Pygott F: Effect of smoking on the production and maintenance of gastric and duodenal ulcers. Lancet 1958; I: 657–666.
46. Boyd EJS, Wilson JA, Wormsley KG: Effects of treatment compliance and overnight gastric secretion on outcome of maintenance therapy of duodenal ulcer with ranitidine. Scand J Gastroenterol 1983; 18: 193–200.
47. Hansen JH, Knigge U: Failure of proximal gastric vagotomy for duodenal ulcer resistant to cimetidine. Lancet 1984; II: 84–86.
48. Okada M, Yao T, Fuchiyami T, Imamura K, Omae T: Factors influencing the healing rate of gastric ulcer in hospitalized

subjects. Gut 1984; 25: 881–885.
49. Zeitoun P, d'Azemar P: International multicentre clinical trial of ranitidine in duodenal ulcer. Comparison with cimetidine. In: Misiewicz JJ, Wormsley KG, eds. The clinical use of ranitidine. Proceedings of the second international symposium on ranitidine. Oxford: Medicine Publishing Foundation, 1982; 143–147.
50. Schiller KFR: Short-term treatment of duodenal ulcer. Comparison of ranitidine with cimetidine. In: Misiewicz JJ, Wormsley KG, eds. The clinical use of ranitidine. Proceedings of the second international symposium on ranitidine. Oxford: Medicine Publishing Foundation, 1982; 157–162.
51. Walt RP, Trotman IF, Frost R, et al: Comparison of twice daily ranitidine with standard cimetidine treatment of duodenal ulcer. Gut 1981; 22: 319–322.
52. Costello FT, Fielding JD, Lee FI: Comparison of ranitidine and cimetidine in short-term healing of duodenal ulcer (abstr). Gastroenterology 1982; 82: 1037.
53. Freitas D, Pontes F, Pinho C, et al: Clinical trial of ranitidine for duodenal ulcer in Portugal (abstr). Scand J Gastroenterol 1982; 17 (suppl 78): 92.
54. Van Dommelen CKV, Stadler FH, Boekhorst JC: Comparison of ranitidine with cimetidine in the treatment of duodenal ulcer. In: Misiewicz JJ, Wormsley KG, eds. The clinical use of ranitidine. Proceedings of the second international symposium on ranitidine. Oxford: Medicine Publishing Foundation, 1982; 154–156.
55. Baar GD, Paris CH, Middleton WRJ, Piper DW: Comparison of ranitidine with cimetidine in duodenal ulcer healing. In: Misiewicz JJ, Wormsley KG, eds. The clinical use of ranitidine. Proceedings of the second international symposium on ranitidine. Oxford: Medicine Publishing Foundation, 1982; 148–153.
56. Lishman AH, Record CO: Ranitidine in the management of duodenal ulceration: controlled and open comparison with cimetidine. In: Misiewicz JJ, Wormsley KG, eds. The clinical use of ranitidine. Proceedings of the second international symposium on ranitidine. Oxford: Medicine Publishing Foundation, 1982; 163–167.
57. Beauidenhout DJJ, Perold JG, Adams G: A comparison of four-week peptic ulcer healing rates following treatment with antacids and ranitidine. S Afr Med J 1984; 65: 1007–1009.
58. Boyd EJS, Wilson JA, Wormsley KG: Maintenance treatment of duodenal and gastric ulcer with ranitidine. In: Riley AJ, Salmon PR, eds. Ranitidine: proceedings of an international symposium held in the context of the seventh world congress of gastroenterology. Amsterdam: Excerpta Medica, 1982; 102–116.
59. Hunt RH, Walt RP, Trotman IF, et al: Comparison of ranitidine, 150 mg nocte, with cimetidine, 400 mg nocte, in the maintenance treatment of duodenal ulcer. In: Misiewicz JJ, Wormsley KG, eds. Clinical use of ranitidine. Proceedings of the second international symposium on ranitidine. Oxford: Medicine Publishing Foundation, 1982; 192–195.
60. Baume PE, Hunt JH: Failure of potent antacid therapy to hasten healing in chronic gastric ulcers. Aus Ann Med 1969; 18: 113–116.
61. Berstad A, Rydning A, Aadland E, Kolstad B, Frislid K, Aaseth J: Controlled clinical trial of duodenal ulcer healing with antacid tablets. Scand J Gastroenterol 1982; 17: 953–959.
62. Butler ML, Gersch H: Antacid versus placebo in hospitalized gastric ulcer patients: a controlled therapeutic study. Am J Dig Dis 1975; 20: 803–807.
63. Doll R, Price AV, Pygott F: Continuous intragastric milk drip in treatment of uncomplicated gastric ulcer. Lancet 1956; I: 70–73.
64. Englert E, Freston JW, Graham DY, et al: Cimetidine, antacid, and hospitalization in the treatment of benign gastric ulcer. Gastroenterology 1978; 75: 416–425.
65. Fedeli G, Anti M, Rapaccini GL, De Vitis I, Butti A, Civello IM: A controlled study comparing cimetidine treatment to an intensive antacid regimen in the therapy of uncomplicated duodenal ulcer. Dig Dis Sci 1979; 24: 758–762.
66. Lam SK, Lam KC, Lai CL, Yeung CK, Yam LY, Wong WS: Treatment of duodenal ulcer with antacid and sulpiride. A double-blind, controlled study. Gastroenterology 1979; 76: 315–322.
67. Littman A, Welch R, Fruin RC, Aronson AR: Controlled trials of aluminum hydroxide gels for peptic ulcer. Gastroenterology 1977; 73: 6–10.
68. LoJudice TA, Saleem T, Lang JA: Cimetidine in the treatment of gastric ulcer induced by steroidal and nonsteroidal anti-inflammatory agents. Am J Gastroenterol 1981; 75: 104–110.
69. Peterson WL, Sturdevant RAL, Frankl HD, et al: Healing of duodenal ulcer with an antacid regimen. N Engl J Med 1977; 297: 341–345.
70. Isenberg JI, Peterson WL, Elashoff JD, et al: Healing of benign gastric ulcer with low-dose antacid or cimetidine. N Engl J Med 1983; 308: 1319–1324.
71. Hollander D, Harlan J: Antacids versus placebo in peptic ulcer therapy. JAMA 1973; 226: 1181–1185.

Critical Care Medicine
Copyright © 1991 by Williams & Wilkins

Vol. 19, No. 7
Printed in U.S.A.

— *Special Article* —

Let's agree on terminology: Definitions of sepsis

ROGER C. BONE, MD, FCCM

"Words mean what I say they mean."
—Humpty Dumpty, from *Alice in Wonderland*

The terms bacteremia, sepsis, septicemia, sepsis syndrome, and septic shock are used interchangeably in speech and in the professional literature. This imprecise terminology causes considerable confusion when used in comparative clinical investigations. Therefore, I propose adoption of a standard, specific nomenclature to denote the various phases of the sepsis process.

Throughout history, the various manifestations of sepsis have proven difficult to diagnose and treat. Precise definitions of these manifestations and a number of related terms (e.g., pyremia), as well as the relationship of these clinical states to standardized laboratory tests (i.e., positive blood cultures) have never been clearly delineated.

Clinical protocols are based on specific criteria that are understood by the developers of that protocol. Inadequate understanding or misunderstanding of definitions can lead to situations in which patients undergo therapeutic protocols that cannot be compared legitimately with other protocols to test the same hypothesis (1–3).

Since there is, as yet, no standardized terminology on the subject of sepsis, and since we must agree on terminology before reliable communication can take place, I have proposed the following framework (Table 1) (4). I offer these as operational definitions. They are not "written in stone." Rather, they would and *should* be changed as data are accumulated and consensus statements are generated.

Bacteremia. According to *Stedman's Medical Dictionary* (11), bacteremia is defined as "the presence of viable bacteria in the circulating blood." Positive blood culture is the diagnostic criterion. Previously, we (7) utilized this definition in a large multicenter study. In that study, one positive blood culture was sufficient to document bacteremia, except when the organism was a likely contaminant such as *Staphylococcus epidermidis*. Under these circumstances, two positive cultures were required.

A 1980 review (12) of Gram-negative bacteremia found that early institution of appropriate antibiotics reduced mortality rate and decreased the frequency of circulatory shock in septic patients by nearly 50%. Therefore, early recognition of bacteremia, especially the Gram-negative species, is essential to the improvement of overall patient survival rates.

Septicemia. Septicemia has been defined as "systemic disease caused by the multiplication of microorganisms in the circulating blood" (13). The term has also been used generically to denote any bloodborne infection. To avoid confusion, the term septicemia should no longer be used.

Sepsis. Sepsis has been defined as "the presence of various pus-forming and other pathogenic organisms, or their toxins in the blood or tissues" (14). I propose that sepsis be defined as in Table 1. Suspicion of infection plus the systemic response to it (tachypnea, tachycardia, and hypothermia or hyperthermia) ought to form the basis of any clinical definition of sepsis.

Although the exact frequency is not known, 70,000 to 300,000 cases of sepsis are estimated to occur in the United States each year (7, 8). Others (5) have estimated that as many as 80,000 Americans die each year from sepsis and its complications. Therefore, it is imperative that we have the ability to understand, assess, and accurately communicate the precise features of a patient's status. Early recognition and treatment are crucial. Once complications of sepsis arise, clinical progression may be rapid and outcome unfavorable.

Several innovations in clinical practice may actually have increased the likelihood of sepsis (8). These factors include aggressive oncologic chemotherapy,

From Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL.

Address requests for reprints to: Roger C. Bone, MD, Department of Internal Medicine, Rush-Presbyterian-St. Luke's Medical Center, 1653 West Congress Parkway, Chicago, IL 60612.

Key Words: adult respiratory distress syndrome; shock, septic; septicemia; renal failure; bacterial infections; Gram-negative bacteria; Gram-positive bacteria; multiorgan failure; nomenclature; terminology

0090-3493/91/1907-0973$03.00/0

Table 1. Proposed delineation of terminology

Term	Definition	Mortality Rate % (Reference)
Bacteremia	Positive blood culture	12 to 61[a] (Young, 1990) (5)
Septicemia	Old term, no longer to be used	
Sepsis	Clinical evidence of infection: Tachypnea (respiration >20 breaths/min; if mechanically ventilated, minute ventilation >10 L/min) Tachycardia (heart rate >90 beats/min) Hyperthermia or hypothermia (core or rectal temperature >101°F [>38°C] or <96.1°F [<35.5°C])	10 to 20[a] (Dunn, 1987) (6) 50 (VA Study, 1987) (3) 20 to 50 (Young, 1990) (5)
Sepsis syndrome	Sepsis, plus evidence of altered organ perfusion (including one or more of the following): Acute changes in mental status Pao_2/Fio_2 ≤280 (without other pulmonary or cardiovascular disease as the cause) Increased lactate (more than upper limits of normal for the laboratory) Oliguria (documented urine output <0.5 mL/kg body weight for at least 1 hr (in patients with bladder catheter in place)	75 (Sprung et al., 1984) (2) 25.6 (Bone et al., 1989) (7)
Septic shock	Sepsis syndrome with hypotension that is responsive to iv fluids or pharmacologic intervention (systolic BP <90 mm Hg *or* decrease in mean arterial pressure by >40 mm Hg from baseline in a hypertensive patient)	40 to 90 (Parker and Parrillo, 1983) (8) 27.5 to 43.2 (Bone et al., 1989) (7) 40 to 50 (Cotran et al., 1989) (9) 10 to 36 (Cunnion and Parrillo, 1989) (10)
Refractory or nonresponsive septic shock	Sepsis syndrome with hypotension that lasts for >1 hr. These changes are *not* responsive to iv fluids (the equivalent of 500 mL of normal saline over 30 mins) or pharmacologic intervention (requiring vasopressors; e.g., dopamine >10 μg/kg·min).	77 (Sprung et al., 1984) (2) 43 (Bone et al., 1989) (7)

[a]Gram-negative sepsis.

corticosteroid or immunosuppressive therapy for organ transplantation or inflammatory diseases, increased survival of patients predisposed to sepsis, and more frequent use of invasive medical procedures (8, 15).

Sepsis Syndrome. We (4, 7) defined the sepsis syndrome as sepsis with evidence of altered organ perfusion. Sepsis syndrome may be manifested as tachycardia, fever or hypothermia, tachypnea, and evidence of inadequate organ perfusion (Table 1). Identical physiologic responses can be produced by Gram-positive and Gram-negative bacteria; by pathogenic viruses, fungi, and rickettsia; and by noninfectious processes (e.g., pancreatitis, trauma). Patients with sepsis and the sepsis syndrome may have positive or negative blood cultures. In our study of the sepsis syndrome, only 45% of the patients had positive blood cultures. The specific etiology of sepsis syndrome should be noted, if known. Also, cultures should be noted as positive or negative; if they were positive, the presumed organism associated with sepsis syndrome, as well as the site of infection, should be documented.

My colleagues and I (1) studied the sepsis syndrome in a group of prospectively evaluated patients that comprised the placebo treatment group of a double-blind study of methylprednisolone use in the sepsis syndrome and septic shock. The purpose of that study was to define the variables of a syndrome that could be distinguished on the basis of readily available, noninvasive clinical criteria at an earlier stage of deterioration than had been previously cited. We hoped to define a point at which therapeutic interventions might be instituted with greatest likelihood for preventing the sequelae of sepsis syndrome, e.g., septic shock and multiorgan failure, and including the adult respiratory distress syndrome (ARDS) (16, 17). Using this definition of sepsis syndrome, we found that 47% of bacteremic patients went on to develop shock, compared with 29.6% of patients who were nonbacteremic (7). Data from the same investigations (18) showed that 25% of the patients developed ARDS, and that 14-day mortality rate within this population was 22%.

Septic Shock. Septic shock is defined as sepsis syndrome with hypotension (systolic BP <90 mm Hg or decrease from baseline systolic BP >40 mm Hg). Shock develops in approximately 40% of septic patients and adversely affects prognosis (12). In our study of shock in the sepsis syndrome, we found that ten (13%) of 77 patients with sepsis syndrome alone died, compared with 38 (34%) of 113 patients who

Table 2. Variables of multiorgan failure

Disseminated intravascular coagulation	A confirmatory test is positive (FDP >1:40 or D-Dimers >2.0) and there are abnormally low values for platelets (or there is a >25% decrease from a previously documented value) and either prolonged prothrombin time or partial thromboplastin time or clinical evidence of bleeding.These abnormalities must occur in the absence of medically significant confounding factors such as liver failure, major hematoma, or anticoagulant therapy.
Adult respiratory distress syndrome	Unexplained hypoxemia in the presence of a predisposing factor such as sepsis. Bilateral pulmonary infiltrates consistent with pulmonary edema *and* Pao_2/Fio_2 <175. These factors must occur in the absence of congestive heart failure or primary lung disease such as pulmonary embolus or bilateral pneumonia. Pulmonary artery occlusion pressure, when measured, must be <18 mm Hg.
Acute renal failure	Serum creatinine becomes abnormal and urinary sodium is >40 mmol/L in a spot specimen, *or* serum creatinine increases by 2.0 mg/dL (176 μmol/L) in a patient with previous renal insufficiency, and is not prerenal in nature (e.g., associated with dehydration or gastrointestinal bleeding) or due to rhabdomyolysis. (It is preferable if no diuretics are given within 2 hrs before obtaining urinary sodium levels.)
Hepatobiliary dysfunction	Serum bilirubin exceeds 2.0 mg/dL (34 μmol/L), and alkaline phosphatase, gamma glutamyl transpeptidase (GGT), SGOT, or SGPT exceed twice the upper limit of normal, in the absence of confounding disease.
Central nervous system (CNS) dysfunction	Glasgow Coma Scale score is <15 in patients with normal baseline CNS function, or at least one point lower than a baseline Glasgow Coma Scale score in patients with baseline CNS impairment. To assess Glasgow Coma Scale scores, patients cannot be treated with paralyzing or sedating agents in sufficient dose to alter their Glasgow Coma Scale scores.

FDP, fibrin degradation products; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

either had shock or who developed the condition after admission to the study.

The older terms "warm shock" and "cold shock" should be discarded, as they no longer apply. Warm shock referred to that phase in which shock is characterized by decreased systemic vascular resistance and increased cardiac output (arteriolar and venular vasodilation, leukocyte aggregation, microembolization, and endothelial cell injury). Progression to cold shock, as evidenced by increased systemic vascular resistance, is rare, since most patients continue to exhibit decreased systemic vascular resistance, even in the late phases of septic shock. Cold shock, apparent as decreased cardiac output, reflects myocardial depression and the systemic response to it (microvascular insufficiency, inadequate blood flow to tissues, increased lactic acid production, severe organ dysfunction, and even death) (19). The term "refractory shock" has been proposed and should be adopted. This term better describes the clinically relevant situation with its higher associated mortality rate. Refractory shock represents septic shock that does not respond to conventional therapy within a specified time. Much of the statistical variability in regard to sepsis mortality is attributable to the fact that, until now, septic shock and refractory shock have been included within the same category.

Arterial blood lactate concentrations have been used as a measure of the severity of perfusion failure and, hence, of shock (20). Reduced cardiac output, velocity of blood flow, and measured plasma volume have also been associated with disproportionate increases in arterial blood lactate concentrations and fatal outcome. Although the use of BP as a monitoring tool can be legitimately criticized, it is readily available in all hospitals and can be uniformly applied.

Our own investigations showed that the diagnosis of sepsis syndrome without septic shock carries with it a mortality rate of approximately 13%. One would expect that for bacteremia and sepsis, the numbers should be lower and those numbers for septic shock or refractory septic shock, much higher. However, it is not surprising that our review of the literature disclosed remarkable disparity in mortality statistics (Table 1). In presenting these mortality data, we have used the authors' definitions of the clinical entity under investigation in each instance. In doing so, it became obvious that investigators did not always refer to the same disease entity when using any given term. If they had been referring to the same clinical condition, it is unlikely that we would see the same mortality rates (e.g., 40%) associated with such clearly disparate clinical conditions as bacteremia on the one hand, and septic shock on the other (Table 1).

Mortality rates ascribed to septic shock range from 10% to 90% (2, 3, 5–10). At least one study (1) documented that treatment in the latter stages of septic shock had limited effect on clinical outcome. A second study of corticosteroid usage in septic shock documented a 75% mortality rate (44 of 59 patients died) (2).

Multiorgan Failure. In the extreme, the septic process has an impact on multiple organ systems. Deleterious effects are evidenced in a variety of organ-specific ways (Table 2). Use of these criteria in conjunction with the clinical criteria proposed above (Table 1) will contribute to greater precision. For example, it has already been shown that the onset of ARDS, acute renal failure, and hepatobiliary dysfunction are identified with extremely poor prognosis (21).

The purpose of this review was to emphasize the importance of definitions in sepsis. However, the severity of the process should also be evaluated, using scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE II) (22).

CONCLUSION

Early recognition of impending circulatory compromise in patients with sepsis may improve survival through rapid and aggressive therapeutic intervention. Recognition requires both detection of the clinical markers of each of these entities and discernment among the subtle and rapidly changing signs and symptoms that herald a downwardly progressing clinical course.

An era promising therapeutic uses of monoclonal antibodies to endotoxin and to cytokines, such as tumor necrosis factor, is at hand. Armed with reasonable and precise definitions to delineate the components of the septic process, we will now be in a better position to intelligently compare studies of a variety of treatment modalities. Appreciation of the pathophysiology of sepsis and the therapeutics for sepsis means that in the future we will be able to begin therapy at an early stage in the disease process, *before* the onset of shock and multiorgan failure. Only through careful and consistent use of terminology can we expect to achieve this kind of discriminating understanding, thereby potentially improving clinical outcomes for patients. Humpty Dumpty would agree.

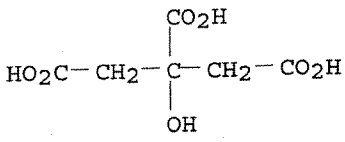
ACKNOWLEDGMENTS

I would like to thank Drs. Eric Rackow and Herman Chmel for their discussion regarding the need for such a statement.

REFERENCES

1. Bone RC, Fisher CJ, Clemmer TP, et al: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:353
2. Sprung CL, Caralis PV, Marcial EH, et al: The effects of high-dose corticosteroids in patients with septic shock: A prospective, controlled study. *N Engl J Med* 1984; 311:1137
3. The Veterans Administration Systemic Sepsis Comparative Study Group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of sepsis. *N Engl J Med* 1987; 317:659
4. Bone RC: Sepsis, sepsis syndrome, multi-organ failure: A plea for comparable definitions. *Ann Intern Med*, In Press
5. Young LS: Gram-negative sepsis. *In:* Principles and Practice of Infectious Diseases. Third Edition. Mandell GL, Douglas RG, Bennet JE (Eds). New York, Churchill Livingstone, 1990, pp 611–636
6. Dunn D: Immunotherapeutic advances in the treatment of Gram-negative bacterial sepsis. *World J Surg* 1987; 11:233
7. Bone RC, Fisher CJ, Clemmer TJ, et al: Sepsis syndrome: A valid clinical entity. *Crit Care Med* 1989; 17:389
8. Parker MM, Parrillo JE: Septic shock: Hemodynamics and pathogenesis. *JAMA* 1983; 250:3324
9. Cotran RS, Kumar V, Robbins SL (Eds): Fluid and hemodynamic derangements. Shock. *In:* Robbins Pathologic Basis of Disease. Fourth Edition. Philadelphia, WB Saunders, 1989, pp 114–120
10. Cunnion RE, Parrillo JE: Myocardial dysfunction in sepsis: Recent insights. *Chest* 1989; 95:941
11. Stedman's Medical Dictionary. 24th Edition. Baltimore, Williams & Wilkins, 1982, p 152
12. Kreger BE, Craven DE, McCabe WR: Gram negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. *Am J Med* 1980; 68:344
13. Stedman's Medical Dictionary. 24th Edition. Baltimore, MD, Williams & Wilkins, 1982, p 1274
14. Stedman's Medical Dictionary. 24th Edition. Baltimore, MD, Williams & Wilkins, 1982, p 1274
15. Shubin H, Weil MH: Bacterial shock. *JAMA* 1976; 235:421
16. Montgomery AB, Stager MA, Carrico CJ, et al: Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985; 132:485
17. Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720
18. Bone RC, Fisher CJ, Clemmer TP, et al: Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. *Chest* 1987; 92:1032
19. Parrillo JE, Parker MM, Natanson C, et al: Septic shock in humans: Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med* 1990; 113:227
20. Rackow EC: Clinical definition of sepsis and septic shock. *In:* New Horizons: Perspectives on Sepsis and Septic Shock. Sibbald WJ, Sprung CL (Eds). Fullerton, CA, Society of Critical Care Medicine, 1986, pp 1–10
21. Bell RC, Coalson JJ, Smith JD, et al: Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med* 1983; 99:293
22. Bihari DJ: Septicaemia—The clinical diagnosis. *J Antimicrob Chemother* 1990; 25(Suppl C):1

RN 57644-54-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, bismuth(3+) potassium salt (2:1:3) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Bismuth subcitrate**
CN CBS
CN Colloidal bismuth subcitrate
CN De-Nol
CN De-Noltab
CN Duosol
CN Duosol (ulcer treatment)
CN Gastrodenol
CN Tripotassium dicitratobismuthate
CN Ulcerone
MF C6 H8 O7 . 1/2 Bi . 3/2 K
CI COM
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, PROMT, RTECS*, SCISEARCH, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (77-92-9)

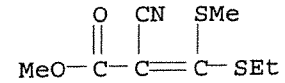


●1/2 Bi(III)

●3/2 K

356 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
356 REFERENCES IN FILE CAPLUS (1907 TO DATE)

AN 1989:450223 CAPLUS
DN 111:50223
TI Gastric antisecretory and antiulcer/cytoprotective effects of 2-cyano-3-(ethylthio-3-methylthio)-2-propenoic acid methyl ester
AU Borella, L. E.; DiJoseph, J. F.
CS Wyeth-Ayerst Res., Inc., Princeton, NJ, USA
SO Arzneimittel-Forschung (**1989**), 39(5), 598-601
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
AB The title compound AY-28,200, inhibited basal and pentagastrin-stimulated gastric acid secretion in the conscious rat (ED50 = 7.6 and 1.9 mg/kg i.g., resp.). For inhibition of basal secretion, peak activity was attained 5-6 h after administration and was maintained for >10 h, with no activity occurring at 24 h. The H+-K+-ATPase activity of rabbit gastric microsomes was inhibited by AY-28,200. AY-28,200 (3 mg/kg, orally) inhibited EtOH-induced gastric lesions. This cytoprotective effect lasted >4 h. AY-28,200 blocked acetylsalicylic acid- and stress-induced gastric **ulcers** but was inactive against indomethacin-induced gastric **ulcers**. AY-28,200 is a parietal cell **proton pump inhibitor** with cytoprotective properties; it may produce its cytoprotective effect by stimulating the formation of endogenous prostaglandins.
IT **121635-47-0**, AY 28200
RL: PRP (Properties)
(antiulcer and gastric-antisecretory effects of)
RN 121635-47-0 CAPLUS
CN 2-Propenoic acid, 2-cyano-3-(ethylthio)-3-(methylthio)-, methyl ester (9CI) (CA INDEX NAME)



IT **9000-83-3**, ATPase
RL: BIOL (Biological study)
(hydrogen ion-potassium-activated, of stomach microsome, AY 28200 inhibition of)

Antacid vs Sucralfate in Preventing Acute Gastrointestinal Tract Bleeding in Abdominal Aortic Surgery

A Randomized Trial in 50 Patients

Edgar Borrero, MD; Joy Ciervo, RN; John B. Chang, MD

• **We carried out a randomized, controlled trial of sucralfate vs antacid as prophylaxis against upper gastrointestinal tract bleeding in 50 patients who had undergone abdominal aortic surgery. The groups were similar in age, sex, duration of prophylaxis, and number of risk factors per patient. No patient in the antacid group had upper gastrointestinal tract bleeding. One patient in the sucralfate group had frank bleeding from the nasogastric tube; however, she also had a coagulopathy and thrombocytopenia. The bleeding stopped when these conditions were corrected. No complications occurred in the sucralfate group; five patients in the antacid group had minor complications. Sucralfate was as effective as antacid in this trial, and it resulted in a considerable saving in nursing time.**
(*Arch Surg* 1986;121:810-812)

We recently reported the effectiveness of sucralfate in preventing acute gastrointestinal tract bleeding in 100 critically ill patients.[1,2] Fatal gastrointestinal tract bleeding in patients who have undergone abdominal aortic surgery is a well-known postoperative complication recently reported to have occurred in three (10.3%) of 29 patients.[4]

It is well known that upper gastrointestinal tract hemorrhage can occur in any patient in the intensive care unit and can lead to the patient's death. Hastings et al,[5] McAlhany et al,[6] and Simonian and Curtis[7] showed that gastrointestinal tract bleeding could be markedly reduced in patients given prophylactic antacid therapy. The side effects associated with antacid therapy (diarrhea and hypermagnesemia) occurred in 25% of the patients.

Sucralfate has been shown to accelerate the healing of mucosal ulcerations by increased generation of the mucosal structures and by stimulating the endogenous mucosal prostaglandin E_2 formation. We conducted a prospective, randomized study to determine if sucralfate would be as effective as antacid in preventing acute gastrointestinal tract bleeding in patients who had undergone abdominal aortic surgery.

PATIENTS AND METHODS

Between August 1983 and December 1984, 50 patients who had undergone abdominal aortic surgery were admitted to the surgical intensive care unit and were randomized to receive either antacid or sucralfate, depending on their year of birth (odd year, sucralfate; even year, antacid). Patients were excluded if they had simultaneously undergone gastric or duodenal surgery, or if they had a history of peptic ulcer disease. Four patients had an initial trace-positive paper (Gastroccult) test, without gross evidence of bleeding due to traumatic passage of the nasogastric tube, and therefore they were included in the study.

Patients randomized to receive sucralfate received 1 g suspended in 30 mL of normal saline solution through the nasogastric tube, followed by 10 mL of normal saline solution to clear the nasogastric tube of any adherent sucralfate every six hours. Hourly pH determinations were performed, but no adjustments in dosage were made. Patients randomized to receive antacid received an initial dose of 30 mL of a commercial antacid (Mylanta II) through

Accepted for publication Oct 8, 1985.

From the Division of Vascular Surgery, Department of Surgery (Drs Borrero and Chang), and the Intensive Care Unit (Ms Ciervo), Long Island Jewish Medical Center, New Hyde Park, NY; and State University of New York at Stony Brook (Drs Borrero and Chang).

Reprint requests to Division of Vascular Surgery, Long Island Jewish Medical Center, New Hyde Park, NY 11042 (Dr Chang).

Table 1.—Principal Diagnoses

Diagnosis	No. of Patients: Sucralfate (N=25)	No. of Patients: Antacid (N=25)
Abdominal aortic aneurysm		
Elective repair	16	18
Rupture	6	3
Aortoiliac occlusive disease	3	4

e nasogastric tube. Each hour, the nasogastric tube was clamped and placed on suction for five minutes. The pH of the astric aspirate was tested. If the pH was less than 3.5, the dosage antacid was progressively doubled until the pH of the subsequent sample aspirate was greater than 3.5. Another antacid (maphojel) was substituted for the first one in patients with severe arrhea or renal failure.

The nasogastric tube was clamped for one hour after administration of the drug to both groups. If regurgitation occurred around e tube or the volume of the aspirate exceeded 150 mL at the end of e one-hour period, the tube was clamped for 30 minutes after ch antacid administration and intermittent suction applied for 30 inutes of each hour until the aspirate was less than 150 mL, when arly instillation of antacid with clamping of the tube for 60 inutes was resumed.

The gastric pH was measured with pH-sensitive paper and corded hourly in both groups. The aspirate was examined for ink or occult blood every hour with the paper test. Any patient io had frank blood in the aspirate or a uniformly dark-blue action on three consecutive readings was considered to have strointestinal tract bleeding, and prophylaxis was deemed a lure. Patients in whom prophylaxis failed were treated with iced line lavage until the aspirate was clear. If the patient had ceived sucralfate, it was discontinued and the antacid regimen gun. If the patient had been receiving antacid, the last dosage as doubled, and the patient continued to receive the doubled dose ery hour. The study was ended when oral feedings were begun, e nasogastric tube was removed, or the patient was discharged m the intensive care unit.

All patients underwent a platelet count and test for prothrombin ne and partial thromboplastin time during the study. All patients ceiving antacid had magnesium levels determined every other y beginning on the second day.

RESULTS

The 25 patients in the sucralfate group (19 men and six omen) had a mean age of 67.9 years. The 25 patients in the tacid group (19 men and six women) had a mean age of 67.1 ars. The principal diagnoses are shown in Table 1. All of e patients had aortobifemoral artery Dacron graft placeent.

Four major risk factors were analyzed in each patient: (1) ajor operative procedure prior to entry into the study, (2) potension, defined as a blood pressure of less than mm Hg for a period greater than 30 minutes, (3) spiratory failure, defined as the requirement for mechanal ventilation with a ratio of arterial oxygen pressure to ced inspiratory oxygen of less than 200 for more than 24 urs, and (4) renal failure, defined as an elevation in serum eatinine value of greater than 3 mg/dL (270 μmol/L) on o successive occasions 24 hours apart.

Table 2.—Characteristics of Study Groups

	Sucralfate (N=25)	Antacid (N=25)
Sex, No. (M/F)	19/6	19/6
Mean age, y	67.9	67.1
No. of risk factors per patient, average	2.39	2.00
No. of deaths	6	1
No. of deaths from gastrointestinal tract bleeding	0	0

There was no statistically significant difference ($P>.05$) between the sucralfate-treated and antacid-treated groups in number of patients, sex, mean age, duration of study per patient (57.6 hours vs 60 hours), or number of risk factors per patient (2.36 vs 2) (Table 2).

No patient in the antacid group had gastrointestinal tract bleeding. One patient in the sucralfate group did have upper gastrointestinal tract bleeding. This patient had undergone an emergency aortobifemoral artery bypass for a ruptured aortic aneurysm. She had frank blood in her gastric aspirate at the 22nd hour after initiation of sucralfate prophylaxis. Her partial thromboplastin time was greater than 100 s, and her platelet count was 49 000/cu mm (49×10^9/L). The bleeding stopped with iced saline lavage and transfusion of fresh frozen plasma and platelets.

There was one death in the antacid group (ruptured aortic aneurysm) and six deaths in the sucralfate group (three elective abdominal aortic aneurysms and three ruptured abdominal aortic aneurysms). Acute upper gastrointestinal tract bleeding did not contribute to any of the deaths.

We were unable to relate any complications to the administration of sucralfate. In the antacid group, four patients had diarrhea and one had reversible hypermagnesemia, for an overall complication rate of 20%. Antacid therapy did not have to be stopped in any patient. No patient had infarction of the left colon.

COMMENT

Sucralfate is a complex of sulfated sucrose and aluminum hydroxide that is not absorbed from the gastrointestinal tract and has negligible acid-neutralizing capacity. Sucralfate binds to both normal gastric mucosa and eroded mucosa, preferentially to the latter. In vitro, the sucralfate-albumin film acts as a barrier to the diffusion of hydrogen ions and pepsin. It absorbs bile and inhibits pepsin. More recently, it has been discovered that sucralfate stimulates a response within the gastroduodenal mucosa, which results in increased regeneration and thickening of the mucosal structure. Sucralfate also increases activity of cells that produce mucus, to create a stronger, thicker mucous layer. Recently, it has been demonstrated that sucralfate induces stimulation of endogenous mucosal prostaglandin E_2 formation, which may, in part, explain its effective cytoprotective properties.[8]

The importance of prophylaxis against gastrointestinal tract bleeding in these critically ill patients is so well established that we thought it inappropriate to test the

action of either of the agen. .gainst a placebo or untreated group.

In the comparison between an antacid regimen for prophylaxis and sucralfate, both agents were found to be equally effective in preventing acute upper gastrointestinal tract bleeding. The costs of the medications are similar; at the time of this study 4 g of sucralfate cost $1.28 and 720 mL of antacid, $1.40. However, with our time table (maintained by the nursing staff during this study), the two regimens differed significantly in the amount of nursing time required for their administration. Sucralfate is dissolved as a single dose every six hours, requires approximately 20 minutes of nursing time per day for suspension and administration, and does not require gastric pH monitoring. Hourly instillations of antacid require gastric pH monitoring and consume a n...mum of 120 minutes of nursing time per d... At the 1983 salary scale for an intensive care unit nurse... our institution, this represents a comparative cost of $3... per day for sucralfate vs $22 per day for antacid.

In addition, the less labor-intensive form of therapy wi... sucralfate is more apt to be fully accomplished in the hig... pressure environment of the intensive care unit than is t... more time-consuming therapy with antacids. Thus, ... conclude that sucralfate represents an excellent alternati... to antacid therapy as prophylaxis against upper gastroi... testinal tract bleeding in patients who have undergo... abdominal aortic surgery. We now routinely use sucralfa... for prophylaxis of gastrointestinal tract bleeding in ... patients who have undergone abdominal aortic surgery.

References

1. Borrero E, Margolis IB, Bank S, et al: A comparison between sucralfate and antacids in the prevention of stress ulcers in critically ill patients, abstracted. *Gastroenterology* 1984;86:1032.
2. Borrero E, Margolis IB, Bank S, et al: A randomized trial of sucralfate vs antacid in preventing acute gastrointestinal bleeding in 100 critically ill patients. *Am J Surg* 1984;148:809-812.
3. Borrero E, Bank S, Margolis IB, et al: A comparison between antacid and sucralfate in the prevention of gastrointestinal bleeding in 155 critically ill patients. *Am J Med* 1985;79:62-64.
4. Hiatt JCG, Barker WF, Machleder HI, et al: Determinants of failure in the treatment of ruptured abdominal aortic aneurysm. *Arch Surg* 1984;119: 1264-1268.
5. Hastings PR, Skillman JJ, Bushnell LS, et al: Antacid titration in ... prevention of acute gastrointestinal bleeding. *N Engl J Med* 1978;2... 1041-1045.
6. McAlhany JC Jr, Czaja AJ, Pruitt BA Jr: Antacid control of compli... tions from acute gastroduodenal disease of burns. *J Trauma* 1976;1... 645-649.
7. Simonian SJ, Curtis LE: Treatment of hemorrhagic gastritis b... antacid. *Ann Surg* 1976;184:429-434.
8. Ligumsky M, Karmelli F, Rochmilewitz D: Sucralfate stimulation ... gastric PGE_2 synthesis: Possible mechanism to explain its effective cytopr... tective properties. Read before the American Gastroenterological Associ... tion, New Orleans, May 20-23, 1984.

SECTION
VIII
Drugs Affecting Gastrointestinal Function

CHAPTER
37 AGENTS FOR CONTROL OF GASTRIC ACIDITY AND TREATMENT OF PEPTIC ULCERS

Laurence L. Brunton

Dyspepsia, in its many forms, has been mankind's companion since the advent of bad cooking, overindulgence, and anxiety. Since one "is not altogether fit for the battle of life who is in perpetual contention with his dinner" (Meredith, 1859), considerable energy has gone into relieving the symptoms of gastric upset and peptic ulcer disease.

For centuries, neutralization of gastric acid with antacids provided the only relief from the pain of ulcers. More recent studies of the physiological control of acid secretion demonstrated that anticholinergic agents would blunt this process. The development by Black and colleagues of antagonists that act at H_2-histaminergic receptors provided a more specific class of inhibitors of gastric acid secretion. The more recent advent of substituted benzimidazole inhibitors of the H^+,K^+-ATPase offers a very effective means of selectively blocking the proton pump that is responsible for acid secretion by the parietal cell. Although gastric acid has dominated thinking about peptic ulcer disease, appreciation of the means by which the gastric mucosa normally protects itself from damage has suggested additional therapeutic approaches (Hornick, 1987; Talley and Ormand, 1989).

The rationale for the use of agents that reduce gastric acidity is best understood in terms of the physiological regulation of acid secretion. A model of the functions of the oxyntic gland in the fundus and corpus of the stomach is shown in Figure 37–1. Although all the anatomical and functional relationships have not been precisely defined, the central role of histamine is evident from the ability of H_2 antagonists to suppress secretory responses to food, gastrin, and vagal stimulation (*see* Black and Shankley, 1987; Wolfe and Soll, 1988). Although mast cells are present in the gastric mucosa, the histamine that is responsible for stimulation of acid secretion appears to arise from endocrine or paracrine cells in the oxyntic gland; these cells express receptors for both muscarinic cholinergic agonists and gastrin, and they secrete histamine in response to activation of these receptors. Gastrin secretion (primarily from the antrum) is stimulated by food, both directly and indirectly (by elevation of gastric pH and by reflexes mediated by the vagus). Although parietal cells also have receptors for gastrin, their response to gastrin is greatly potentiated when H_2 receptors are activated concomitantly. Thus, histamine both transmits and facilitates the stimulation of acid secretion by gastrin.

Histamine plays a similar dual role in acid secretion evoked by stimulation of the vagus, but the anatomical relationships are less clearly defined. In addition to the effects that are mediated by gastrin, vagal stimulation produces an increased secretion of histamine and gastric acid that can be blocked by either nicotinic or M_1-muscarinic antagonists (*e.g.*, pirenzepine). Moreover, cholinergic agonists can exert powerful stimulatory effects on acid secretion in the presence of H_2 antagonists through interaction with muscarinic receptors on parietal cells; the receptor subtype that mediates this response has not been firmly established (*see* Chapters 5 and 6). Evidently, endogenous ACh has only limited access to parietal cells, apparently because it is released from postganglionic neurons that are closer

to endocrine than to parietal cells. It is not clear how transmission from the vagus to these postganglionic neurons is accomplished; the potent blocking effects of pirenzepine are also unexplained, in part because the type of muscarinic receptor on the endocrine cells has not been defined.

Stimulation of H_2 receptors on parietal cells causes activation of adenylyl cyclase (*see* Chapter 2), and a complex array of morphological and biochemical changes ensues (*see* Sachs *et al.*, 1988; Forte *et al.*, 1989). Although the sequence of events is not completely known, mediation by adenosine 3′,5′-monophosphate (cyclic AMP) has been established. An increase in the concentration of cytosolic Ca^{2+} is also involved, and stimulation of parietal cells by cholinergic agonists elevates intracellular Ca^{2+} and stimulates nearly maximal rates of acid secretion (without a change in cyclic AMP). Ultimately, the most important consequence of these early events is the activation of a unique H^+,K^+-ATPase and its insertion into the membrane of the apical canaliculus of the parietal cell. This enzyme catalyzes the exchange of intracellular H^+ for extracellular K^+, and, with the concomitant increase in the permeability of the apical membrane to K^+ and Cl^-, about 0.1 N HCl accumulates in the lumen of the canaliculus. The human stomach is capable of producing 20 to 40 mEq of HCl per hour; this capacity accounts for the use of 960 mEq of antacid per day in many therapeutic regimens. Inhibitors of the H^+,K^+-ATPase, such as omeprazole, can virtually eliminate acid secretion.

Stimuli for acid secretion also enhance the secretion of mucus and bicarbonate, which serve to pro-

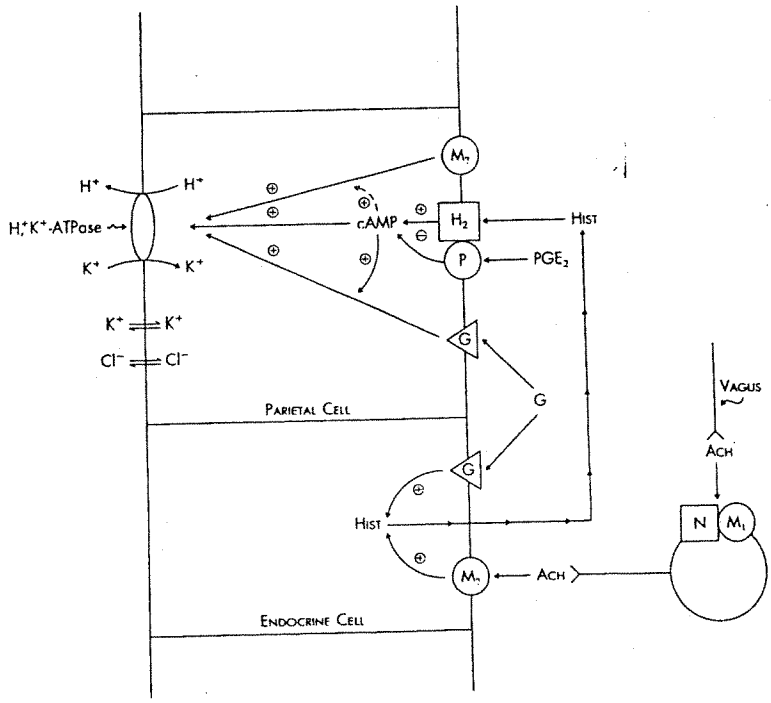


Figure 37–1. *Regulation of acid secretion by the parietal cell.*

ACH = acetylcholine; G = gastrin; HIST = histamine; cAMP = cyclic AMP; PGE_2 = prostaglandin E_2; ⊕ = stimulation; ⊖ = inhibition; H_2 = H_2 histamine receptor; G = gastrin receptor; P = prostaglandin receptor; N = nicotinic cholinergic receptor; M = muscarinic cholinergic receptor. The muscarinic receptors in parietal and endocrine cells have not been fully characterized. *See* text for detailed description.

tect the gastric mucosa from damage. To an important degree, this "cytoprotective" function is mediated by the elaboration of prostaglandins such as PGE_2, which also participate in feedback regulation of acid secretion by inhibition of both adenylyl cyclase activity and the release of gastrin. Interference with the protective functions of prostaglandins by inhibition of their synthesis is thought to account for much of the ulcerogenic effect of aspirin-like drugs. Although enhancement of cytoprotection might provide an alternative method for treatment of peptic ulcers, such use of analogs of PGE_2 (*e.g.*, misoprostol) appears to be effective only when there is substantial inhibition of the secretion of acid.

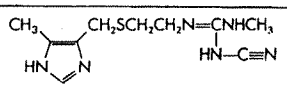
H_2-RECEPTOR ANTAGONISTS

The inability of H_1 antagonists to inhibit gastric acid secretion, including that elicited by histamine, has long been known. However, the development in the 1970s of H_2 antagonists provided incontrovertible evidence for the importance of endogenous histamine in the physiological control of gastric secretion (*see* Figure 37–1; *see also* Chapter 23).

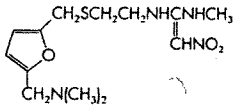
Chemistry. The H_2 antagonists in clinical use are analogs of histamine that contain a bulky side chain in place of the ethylamine moiety. Early representatives of the group, such as burimamide (Black *et al.*, 1972) and cimetidine (the first compound released for general use) retain the imidazole ring of histamine. This ring is replaced in more recently developed compounds by a furan (ranitidine) or a thiazole (famotidine, nizatidine). The structures of H_2 antagonists that are currently available are presented in Table 37–1. As a group, these drugs are more hydrophilic than are the H_1 antagonists, and they reach the central nervous system (CNS) to only a limited extent.

Pharmacological Properties. H_2 antagonists inhibit competitively the interaction of histamine with H_2 receptors. They are highly selective and have little or no effect on H_1 or other receptors. Although H_2 receptors are present in numerous tissues, including vascular and bronchial smooth muscle, H_2 antagonists interfere remarkably little with physiological functions other than gastric secretion. Nevertheless, they measurably inhibit effects on the cardiovascular and other systems that are elicited through H_2 receptors by exogenous or endogenous histamine (*see* Brogden *et al.*, 1982; Ganellin and Parsons, 1982).

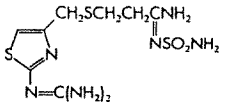
Table 37–1. STRUCTURES OF H_2 ANTAGONISTS



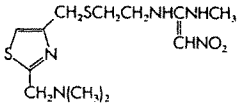
Cimetidine



Ranitidine



Famotidine



Nizatidine

Gastric Secretion. H_2 antagonists inhibit gastric acid secretion elicited by histamine and other H_2 agonists in a dose-dependent, competitive manner; the degree of inhibition parallels the concentration of the drug in plasma over a wide range (Figure 37–2). The H_2 antagonists also inhibit acid secretion elicited by gastrin and, to a lesser extent, by muscarinic agonists. Importantly, these drugs inhibit basal (fasting) and nocturnal acid secretion and that stimulated by food, sham feeding, fundic distention, and various pharmacological agents; this property reflects the vital role of histamine in mediating the effects of diverse stimuli (*see* Figure 37–1). The H_2 antagonists reduce both the volume of gastric juice secreted and its H^+ concentration. The output of pepsin, which is secreted by the chief cells of gastric glands (mainly under cholinergic control), generally falls in parallel with the reduction in volume of gas-

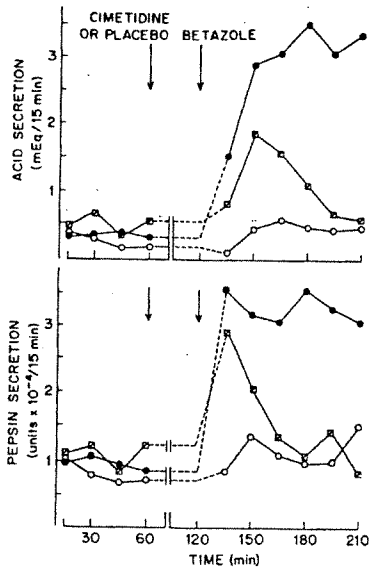


Figure 37–2. *Effect of cimetidine on betazole stimulation of secretion of acid (upper panel) and of pepsin (lower panel) in man.*

A placebo (•) or cimetidine (200 mg, ⌀; 300 mg, ○) was given orally 1 hour before the subcutaneous administration of betazole (1.5 mg/kg). (Modified from Binder and Donaldson, 1978.)

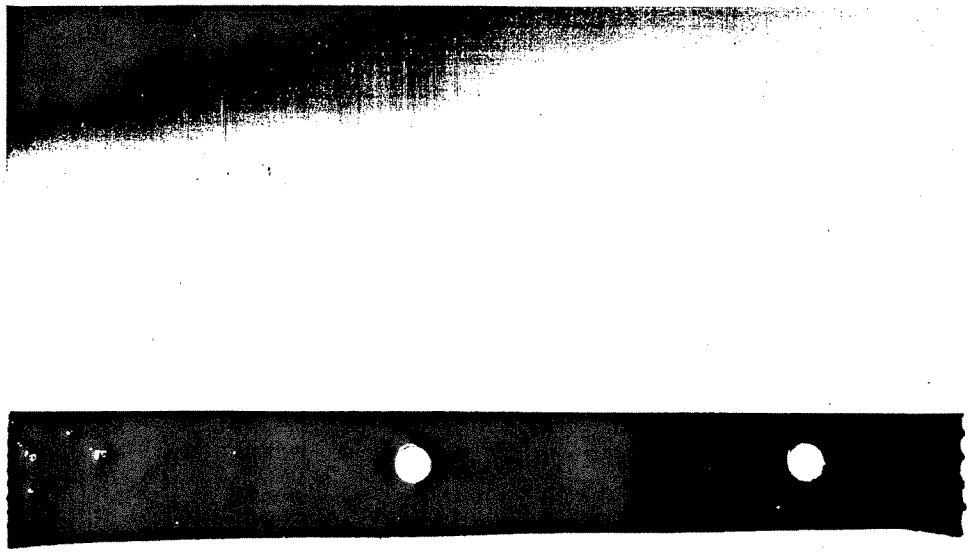
tric juice (*see* Figure 37–2). Secretion of intrinsic factor is also reduced; however, since this protein is normally secreted in great excess, absorption of vitamin B_{12} is usually adequate even during long-term therapy with H_2 antagonists. The concentration of gastrin in plasma is not significantly altered under fasting conditions, although the normal prandial elevation may be augmented; this increase is apparently a consequence of reduction of the feedback inhibition of gastrin secretion that is normally provided by H^+.

H_2 antagonists protect experimental animals from gastric ulceration induced by stress, pyloric ligation, aspirin, H_2 agonists, or cholinomimetics. H_2 antagonists also counter peptic ulceration in man, as described below. They have no consistent effect on the rate of gastric emptying, the pressure of the lower esophageal sphincter, or pancreatic secretion.

Absorption, Fate, and Excretion. As a group, H_2 antagonists are rapidly and well absorbed after oral administration; peak concentrations in plasma are attained within 1 or 2 hours. The oral bioavailability of nizatidine approximates 90%, whereas first-pass hepatic metabolism limits the bioavailability of the other compounds to about 50%. The half-time for elimination of cimetidine, ranitidine, and famotidine is 2 to 3 hours, while that of nizatidine is somewhat shorter—about 1.3 hours. These drugs are in large part excreted in the urine without being metabolized. However, the half-life of ranitidine is significantly prolonged in patients with hepatic dysfunction.

Adverse Effects. A variety of adverse reactions have been ascribed to cimetidine and ranitidine, reflecting, in part, the very large number of patients who have been treated with these drugs. The incidence of reactions is low, and they are generally minor. The low incidence is attributable in part to the limited function of H_2 receptors in organs other than the stomach and to the poor penetration of these agents across the normal blood–brain barrier. The profoundly hypochlorhydric stomach favors the formation of bezoars and the survival of microorganisms; the latter may explain rare cases of candidal peritonitis. Reduction of gastric acidity by H_2 antagonists can also impair the absorption of nonheme dietary iron, but this effect is generally without significance.

The incidence of adverse effects with cimetidine is about 5%; reactions are usually less intense with the other drugs, and some are not produced at all. The most common side effects of cimetidine are altered laxation, headache, dizziness and nausea, myalgia, skin rashes, and itching. The incidence of symptoms related to the CNS appears to be higher in the elderly and in patients with impaired renal function. Loss of libido, impotence, and gynecomastia are sometimes observed in patients who receive long-term therapy with high doses of cimetidine. These effects are presumably related to the ability of the drug to enhance the secretion of prolactin and to bind to



androgen receptors. In addition, cimetidine inhibits the cytochrome P_{450}–catalyzed hydroxylation of estradiol and increases the plasma concentration of estradiol in men (Gailbraith and Michnovicz, 1989). These effects on male sexual function are not shared by the other agents. Case reports suggest that cimetidine occasionally causes hematological effects (various cytopenias) and altered function of the immune system. Rarely, the use of cimetidine has been associated with reversible bone marrow depression, hepatitis, or anaphylaxis. Cimetidine appears to inhibit competitively the renal tubular secretion of creatinine and causes a small increase in its plasma concentration. Rapid intravenous infusion of H_2 antagonists has caused bradycardia and release of histamine. (For reviews of the adverse effects of H_2 antagonists, *see* Zeldis *et al.*, 1983; Powell and Donn, 1984; and Aymard *et al.*, 1988.)

Drug Interactions. All agents that inhibit gastric acid secretion may alter the bioavailability and rate of absorption of certain drugs secondary to changes in gastric pH (*see* below).

Cimetidine (but not the other H_2 blockers) inhibits the activity of cytochrome P_{450}, thereby slowing the metabolism of many drugs that are substrates for hepatic mixed-function oxidases. Thus, the concurrent administration of cimetidine will prolong the half-life of a host of drugs, including warfarin, phenytoin, theophylline, phenobarbital, many benzodiazepines, propranolol, nifedipine, digitoxin, quinidine, mexiletine, and tricyclic antidepressants such as imipramine. Such interactions may require either reduction of dosage or alteration of the regimen. (The drug interactions of H_2 antagonists have been reviewed by Sedman, 1984; Nazario, 1986; and Aymard *et al.*, 1988.)

Preparations, Routes of Administration, and Dosage. H_2 antagonists are well tolerated and can be administered in doses well in excess of those needed to produce an effect. Thus, despite their short half-lives in plasma, these drugs can often be taken only once or twice daily (the "maximal dose" strategy).

Cimetidine (TAGAMET) is available for oral use as tablets containing 200, 300, 400, or 800 mg and as a liquid containing 300 mg/5 ml. For treatment of active duodenal or benign gastric ulcers, the recommended dosage is 800 mg at bedtime. Alternatively, 300 mg four times a day or 400 mg twice daily may be used. Treatment is usually continued for 4 to 8 weeks; however, a dose of 400 mg may be given at bedtime for prevention of recurrence of duodenal ulcers. Solutions of the hydrochloride salt of cimetidine (6 or 150 mg/ml) are available for intramuscular or intravenous administration.

Ranitidine hydrochloride (ZANTAC) is available in tablets (150 or 300 mg) and as a syrup (15 mg/ml) for oral use. The usual dosage schedule for treatment of active duodenal ulcer is 150 mg twice daily or 300 mg at bedtime. Injectable solutions (0.5 or 25 mg/ml) are also available; 50 mg can be given intramuscularly or by intravenous infusion every 6 to 8 hours.

Famotidine (PEPCID) is available in tablets (20 or 40 mg), an oral suspension (40 mg/5 ml), and a solution (10 mg/ml) for intravenous injection. For acute duodenal ulcer, 40 mg at bedtime or 20 mg twice daily is recommended.

Nizatidine (AXID) is supplied as 150-mg and 300-mg capsules for oral use. The recommended dosage for active duodenal ulcer is 300 mg at bedtime or 150 mg twice a day.

Therapeutic Uses. The clinical use of H_2 antagonists stems largely from their capacity to inhibit gastric acid secretion, especially in patients with peptic ulceration. In appropriate doses, the various H_2 antagonists appear to produce equivalent therapeutic responses, although they differ in their propensity to cause adverse reactions.

Duodenal Ulcer. H_2 antagonists profoundly lower basal and nocturnal secretion of acid and that stimulated by meals and other factors; they reduce both the pain of duodenal ulcer and the consumption of antacids, and they hasten healing. Duodenal ulcers usually heal within 4 to 6 weeks of treatment, but 8 weeks is sometimes required. About 10% of patients do not respond in this period of time, and more prolonged treatment with H_2 antagonists is then of questionable value. Although similar rates of healing can be achieved by the vigorous administration of antacids, H_2 antagonists are more conveniently administered and lack pronounced effects on bowel motility. After successful treatment, ulcers recur within a year in about 50% of patients; this rate can be reduced to about 20% by the administration of maintenance doses of an H_2 antagonist once daily at bedtime.

Gastric Ulcer. H_2 antagonists also accelerate the healing of benign gastric ulcers; treatment for 8 weeks is sufficient for 50 to 75% of patients. The drugs also markedly reduce the rate of relapse when given in maintenance doses at bedtime.

Zollinger–Ellison Syndrome. In this disease, a non–beta cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate secretion of gastric acid to life-threatening levels;

H_2 antagonists provide valuable treatment. However, very high doses of these agents are necessary, and adequate suppression of acid secretion may not be achieved (Jensen *et al.*, 1983). Newly developed inhibitors of the H^+,K^+-ATPase appear to be of particular value in this condition (*see* below).

Other Conditions. H_2 antagonists may be useful whenever it is appropriate to reduce gastric acid secretion. Such conditions include reflux esophagitis, stress ulcers, short-bowel (anastomosis) syndrome, and hypersecretory states associated with systemic mastocytosis or basophilic leukemia with hyperhistaminemia. They are also used as a preanesthetic medication in emergency operations to reduce the danger of aspiration of acidic gastric contents (Baron, 1981; Brogden *et al.*, 1982; Riley and Salmon, 1982; Zeldis *et al.*, 1983).

Most patients with acute urticaria respond well to administration of H_1 histaminergic antagonists (*see* Chapter 23). However, a small number of these individuals develop chronic urticaria that is refractory to both H_1 antagonists and to all efforts to eliminate exposure to potential allergens. An ill-defined percentage of these patients appears to respond well to the concurrent administration of both an H_1 and an H_2 antagonist (Bleehen *et al.*, 1987). This effect is presumed to reflect some contribution to the condition from H_2 receptors in the cutaneous microvasculature.

INHIBITORS OF H^+,K^+-ATPASE

The ultimate mediator of acid secretion is the H^+,K^+-ATPase ("proton pump") of the apical membrane of the parietal cell (*see* Figure 37–1). A number of specific inhibitors of this unique enzyme have been developed; a family of substituted benzimidazoles were discovered first, and one of these compounds, omeprazole, has been released for clinical use (*see* Sachs *et al.*, 1988). These agents offer a means to inhibit acid secretion to any desired level. They are especially useful in patients with hypergastrinemia and may be valuable in those

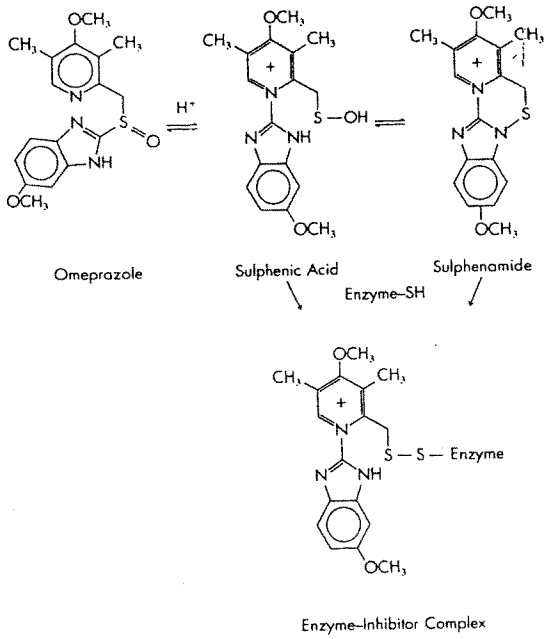


Figure 37–3. *Chemical reactions of omeprazole that lead to inhibition of H^+,K^+-ATPase. See* text for explanation.

whose peptic ulcer disease is not well controlled by H_2 antagonists.

Chemistry and Mechanism of Action. The prototypical compound, omeprazole, contains a sulfinyl group in the bridge that links substituted benzimidazole and pyridine rings (Figure 37–3). Omeprazole is chemically stable and devoid of inhibitory activity at neutral pH. However, the compound is protonated at pH 5 and below and rapidly rearranges to two species, a sulphenic acid and a sulphenamide, that react with sulfhydryl groups in the enzyme. Complete inhibition occurs when two reactive molecules derived from omeprazole are bound to each molecule of enzyme through disulfide linkages.

The selective distribution of the H^+,K^+-ATPase and the requirement for an acidic environment to generate the active forms of omeprazole lend a high degree of specificity to its action. The active species are permanent cations, and they are concentrated within the highly acidic lumen of the parietal cell canaliculi, adjacent to the luminal face of the target enzyme. The reaction shown in Figure 37–3 results in permanent inhibition of enzyme activity *in vivo*, and secretion of acid resumes only after insertion of new molecules of H^+,K^+-ATPase into the luminal membrane (*see* Lindberg *et al.*, 1987; Sachs *et al.*, 1988; Forte *et al.*, 1989).

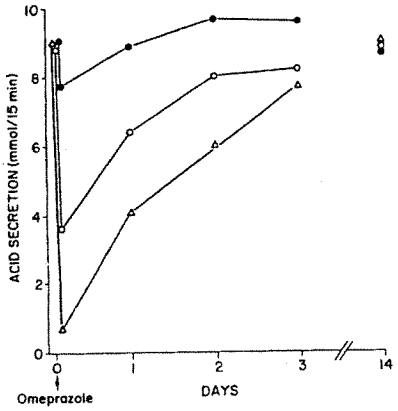


Figure 37–4. *Inhibitory effect of omeprazole on secretion of gastric acid in man.*

Maximal secretory responses were elicited in six healthy human subjects by infusing pentagastrin (91 μg) over a 1-hour period before and at various intervals after a single oral dose of omeprazole (○, 20 mg; △, 40 mg) or placebo (●). Note the profound and prolonged inhibition. (Modified from Lind *et al.*, 1983.)

Pharmacological Properties. The pharmacological effects of omeprazole are largely confined to inhibition of gastric acid secretion and effects that result therefrom. Omeprazole produces only small and inconsistent changes in the volume of gastric juice or in the secretion of pepsin and intrinsic factor; gastric motility is not affected.

Omeprazole produces a dose-related inhibition of gastric acid secretion that persists after the drug disappears from the plasma (Figure 37–4). Given in sufficient dosage (*e.g.*, 30 mg per day for 7 days), omeprazole can reduce the daily production of acid by more than 95%; pretreatment values are not achieved until 4 or 5 days after withdrawal of the drug, presumably reflecting the time required to synthesize the protein. One consequence of profound reduction in gastric acidity is increased secretion of gastrin, and patients who take the usual therapeutic dose of omeprazole have a modest hypergastrinemia. Prolonged administration of very high doses of omeprazole to experimental animals causes hyperplasia of oxyntic mucosal cells, presumably because of trophic effects of gastrin on these cells; carcinoid tumors are also produced in rats. Although no evidence of mucosal proliferation has been found in human subjects, many clinicians are unwilling to administer omeprazole for longer than 8 weeks if suitable alternative therapy is available. The pharmacological properties of omeprazole have been reviewed by Clissold and Campoli-Richards (1986) and by Adams and coworkers (1988).

Absorption and Fate. Orally administered omeprazole is absorbed rapidly but to a variable extent; its bioavailability depends upon dose and gastric pH, and it may reach 70% with repeated administration. These properties presumably reflect the lability of the drug in acid and its impact on gastric pH. It is extensively (more than 95%) bound to plasma protein. Omeprazole is cleared from the circulation by hepatic metabolism with a half-time of 30 to 90 minutes; most of the metabolites are excreted in the urine (*see* Clissold and Campoli-Richards, 1986).

Adverse Effects. Omeprazole is generally well tolerated, and treatment of pa-

tients with Zollinger–Ellison syndrome with doses of 180 to 360 mg per day for up to 4 years has not caused serious side effects (*see* Adams *et al.*, 1988). About 3% of patients experience gastrointestinal effects, including nausea, diarrhea, and abdominal colic; CNS effects (*e.g.*, headache, dizziness, somnolence) have been reported less frequently. Skin rash, leukopenia, and transient elevations of plasma activities of hepatic aminotransferases have been observed occasionally. Although not yet noted with omeprazole, bacterial overgrowth in the gastrointestinal tract and development of nosocomial pneumonia are potential risks of long-term elevation of gastric pH.

Drug Interactions. Since omeprazole interacts with cytochrome P_{450} *in vitro*, inhibition of hepatic metabolism of certain drugs may be of potential importance. Although the clearance of diazepam is reduced by about 50%, omeprazole has only minor effects on the elimination of single oral doses of phenytoin.

Preparations and Dosage. Omeprazole (LOSEC) is supplied in 20-mg tablets for oral use. The dosage for the treatment of gastric or duodenal ulcers or reflux esophagitis is 20 to 40 mg given once daily in the morning for up to 8 weeks. The long-term management of patients with Zollinger–Ellison syndrome may require more than 120 mg of omeprazole per day given in two or three divided doses.

Therapeutic Uses. Omeprazole promotes healing of ulcers in the stomach, duodenum, and esophagus. It is of particular value in the treatment of patients who do not respond adequately to H_2 antagonists, especially those with Zollinger–Ellison syndrome (*see* Adams *et al.*, 1988).

Peptic Ulcers and Reflux Esophagitis. The administration of 20 to 30 mg of omeprazole per day produces about the same rate of healing of benign gastric ulcers as do usual therapeutic doses of either cimetidine or ranitidine; daily doses of 40 mg produce faster rates of healing and reduced rates of relapse (Walan *et al.*, 1989). Although relief of pain may occur more rapidly, most studies of patients with duodenal ulcers indicate that omeprazole (20 to 40 mg daily) is equivalent to the H_2 antagonists in rates of healing and relapse. By contrast, omeprazole is appreciably more effective than H_2 antagonists in the treatment of reflux esophagitis.

Zollinger–Ellison Syndrome. The peptic and esophageal ulceration associated with gastrin-producing tumors is often difficult to treat. Long-term studies indicate that chronic administration of omeprazole promotes healing and suppresses recurrence of ulcers in patients with this condition. The goal of therapy is to reduce the basal secretion of acid to below 10 mEq per hour. This usually requires administration of 60 to 70 mg of omeprazole per day; 90% of patients are controlled with daily doses of 120 mg.

ANTACIDS

Antacids are basic compounds that neutralize acid in the gastric lumen. The substantial incidence of placebo effects in individuals with minor gastrointestinal upsets, and even with peptic ulcer, deludes the self-medicating laity and often the physician into inappropriate use of antacids. Even when indicated, antacids are frequently used in quantities insufficient for optimal effect.

Chemistry. Antacids are compared quantitatively in terms of their acid-neutralizing capacity, defined as the quantity of 1 N HCl (expressed in milliequivalents) that can be brought to pH 3.5 in 15 minutes. The time limit reflects the fact that some formulations may react with acid so slowly that a negligible amount is neutralized during the sojourn of the preparation in the stomach.

Although the basic anions used in antacids include carbonate, bicarbonate, citrate, phosphate, and trisilicate, hydroxide is the most commonly employed. The antacid properties and therapeutic suitability of a product are also greatly influenced by the metallic cation. Aluminum and magnesium hydroxides are the usual preparations. The hydroxides of the alkali metals are completely ionized in water and are thus too strongly basic for clinical use. The solubility of $Mg(OH)_2$ is very low; consequently, OH^- does not accumulate to a concentration that would be corrosive. Nevertheless, $Mg(OH)_2$ is quite reactive with H^+, and it is the most rapidly acting of the insoluble antacids. $MgCO_3$ is much more soluble, yet it reacts less rapidly with acid because of its crystalline structure. Magnesium trisilicate is a relatively poor antacid that reacts only slowly with HCl to form silicon dioxide hydrate. Thus, the stomach may empty before significant neutralization occurs.

$Al(OH)_3$ is also relatively insoluble. The rate of neutralization of acid by $Al(OH)_3$ is considerably slower than that achieved with $Mg(OH)_2$, $MgCO_3$, or $CaCO_3$, and it varies with the method of preparation. Because of complexities of the chemistry of hydrated Al^{3+}, even the most reactive $Al(OH)_3$ cannot elevate the pH much above 4.5. An important chemical property of Al^{3+} in the intestinal milieu is its capacity to form insoluble salts with dietary phosphate.

$CaCO_3$ neutralizes HCl rapidly and effectively; the rate depends on the particle size and crystal structure of the preparation. The liberated Ca^{2+}

may enter into other chemical reactions in the duodenum and in the more alkaline environment of the small intestine, including the formation of insoluble calcium phosphates and calcium soaps.

PHARMACOLOGICAL PROPERTIES

Gastrointestinal Effects. *Intragastric pH.* The acid-neutralizing properties of antacids in the stomach roughly parallel those observed *in vitro*. The pH achieved depends on the form and dosage of the antacid and on whether the stomach is full or empty. The presence of food alone elevates gastric pH to about 5 for approximately 1 hour. Meals prolong the neutralizing effects of antacids for about 2 hours; the compounds are cleared from the empty stomach in about 30 minutes.

Mucoproteins and other substances tend to slow the rate of neutralization and decrease the acid-neutralizing capacity, especially of $Al(OH)_3$. In addition, the rate of neutralization of gastric acid by $Al(OH)_3$ is usually too slow relative to gastric emptying time to neutralize gastric acid when the stomach is empty. The concurrent use of $Mg(OH)_2$ and $Al(OH)_3$ provides both a fast-acting component, which can achieve neutralization within a few minutes, and a more sustained effect. Food in the stomach delays emptying and allows more time for $Al(OH)_3$ to react.

Antipeptic Effects. Partial neutralization of human gastric juice can *increase* its peptic activity. At pH 2, peptic activity is nearly four times that at pH 1.3. Its activity declines as the pH rises further, but active proteolysis occurs until the pH exceeds 5. Pepsin becomes irreversibly inactivated as the pH approaches neutrality. In addition, the autocatalytic activation of pepsin from pepsinogen is initiated by acid. Thus, reduction of gastric acidity will also suppress activation of pepsin. In addition, Al^{3+}-containing antacids may have direct antipeptic effects because of the reversible adsorption of pepsin to particles of $Al(OH)_3$ above pH 3 (*see* Berstad, 1982a).

Effects on Acid Secretion. Elevation of the pH in the gastric antrum increases the secretion of gastrin and causes a compensatory secretion of acid and pepsin. In normal individuals, the effect of gastric alkalinization on acid secretion after a meal appears to be small. In patients with duodenal ulcer, the effect of $NaHCO_3$ may be quite pronounced; maintenance of a continuous pH over 5.5 may double the acid secretion caused by a meal.

Once intragastric pH has been increased by antacids, gastric acid secretion persists even after the pH has returned to a value that normally terminates the antral secretion of gastrin. This "rebound" secretion is brief and of a low degree after ingestion of $Al(OH)_3$, $Mg(OH)_2$, or $NaHCO_3$, but it is prolonged and relatively intense after large doses (*e.g.*, more than 1 g) of $CaCO_3$. The greater acid rebound after $CaCO_3$ probably results from stimulatory effects of Ca^{2+} on the secretion of gastrin and HCl (*see* Holtermüller and Dehdaschti, 1982).

Gastrointestinal Motor Activity. Alkalinization of the gastric contents increases gastric motility through the action of gastrin. However, Al^{3+} can relax the smooth muscle of the stomach and delay gastric emptying, effects that are diminished by Mg^{2+}. Thus, $Al(OH)_3$ and $Mg(OH)_2$ taken concurrently have relatively little effect on gastric emptying (Lux *et al.*, 1982). Alkalinization of the gastric contents also increases lower esophageal pressure and esophageal clearance.

Antacids affect bowel motility and secretions. Magnesium salts cause laxation and are frequently used for that effect (*see* Chapter 38). Laxation is sometimes attributed to an osmotic effect, but Mg^{2+} also stimulates the secretion of cholecystokinin, which may contribute to the increased motor activity. Aluminum compounds cause constipation. Most commercial antacids contain mixtures of aluminum and magnesium compounds and usually do not change bowel function drastically. Nevertheless, the ratio of components varies considerably among individual products and the outcome is often unpredictable. Because of its capacity to enhance secretion and to form insoluble compounds, $CaCO_3$ has complex effects: it is variously described as causing laxation or constipation (*see* Clemens and Feinstein, 1977; Holtermüller and Dehdaschti, 1982; Ström, 1982).

Miscellaneous Gastrointestinal Effects. Al^{3+} may stimulate mucus secretion, an effect that would enhance the mucosal barrier to acid (*see* Caspary, 1982). In the gut, antacids form insoluble compounds with numerous substances, thereby interfering with their absorption. For example, Al^{3+} and Ca^{2+} form insoluble phosphates and Ca^{2+} forms insoluble CaF_2, thereby decreasing the bioavailability of dietary phosphate and fluoride. Ingestion of large amounts of Ca^{2+}-containing antacids can contribute to the milk-alkali syndrome (*see* below).

Al^{3+}-containing antacids adsorb bile acids, lysolecithin, and various proteins, such as pepsin (*see* above). Furthermore, Al^{3+} is strongly astringent, precipitates many proteins, and can react with fatty acids to form hydrophobic soaps. $CaCO_3$ and $Mg(OH)_2$ have weaker adsorptive activity than $Al(OH)_3$, and Ca^{2+} and Mg^{2+} are also less astringent than Al^{3+}.

Absorption, Distribution, and Excretion. *Effect of Absorption on Acid–Base Balance.* Antacids vary in the extent to which they are absorbed. Unneutralized $NaHCO_3$ and sodium citrate are completely absorbed and cause transient metabolic alkalosis. Antacids that are neutralized in the stom-

ach may also disturb systemic acid–base balance. Normally, gastric HCl is neutralized by enteric $NaHCO_3$, such that there is no net effect on the overall acid–base balance. Exogenous antacid upsets this cycle by neutralizing the HCl and permitting absorption of the spared enteric $NaHCO_3$.

Antacids that contain aluminum, calcium, or magnesium are less completely absorbed than those that contain $NaHCO_3$ or sodium citrate. Unreacted insoluble antacids pass through the intestines largely as such and are eliminated in the feces. When the products from reacted antacids enter the intestine, some of the cations are absorbed. Unabsorbed cation may not spare enteric $NaHCO_3$, because an equivalent amount of HCO_3^- or CO_3^{2-} is consumed in the formation of insoluble hydroxides or carbonates. For example, Ca^{2+} reacts with CO_3^{2-} in the small intestine to form $CaCO_3$. The equivalent of $2HCO_3^-$ is thus retained in the gut, and there is no net change in overall acid–base balance. Al^{3+} may be excreted as aluminum carbonates, aluminum hydroxide, and oxyaluminum hydroxide. Mg^{2+} is eliminated in the feces as $Mg(OH)_2$ and as soluble salts, such as the chloride and bicarbonate. Small amounts of the cations from the insoluble antacids are eliminated as soaps, phosphates, and sundry other insoluble compounds.

Aluminum-Containing Antacids. Dietary intake of Al^{3+} is normally in the range of 10 mg daily, of which about 0.1% is absorbed. Use of antacids considerably increases this load, and about 0.1 to 0.5 mg of the cation may be absorbed from a standard daily dose of an Al^{3+}-containing antacid, depending on dietary factors (Weberg and Berstad, 1986). In persons with normal renal function, ingestion of Al^{3+}-containing antacids leads to about a doubling of the average concentration of Al^{3+} in plasma. Since Al^{3+} is eliminated in the urine, plasma concentrations rise in renal failure and toxicity can occur (*see* below). The absorption, distribution, and excretion of aluminum have been reviewed in detail by Alfrey (1983).

Calcium-Containing Antacids. The fraction of Ca^{2+} absorbed from $CaCO_3$ averages 15% in normal patients and seems to vary in proportion to gastric acid secretion. A dose–absorption relationship has not been established for $CaCO_3$; however, by analogy with other forms of Ca^{2+}, the amount absorbed probably reaches a plateau at a daily dose of about 20 g of Ca^{2+}. Dietary factors such as the content of fat alter Ca^{2+} absorption, and it is also regulated by several hormones (*see* Chapter 62).

Hypercalcemia is only transient after a single dose of a Ca^{2+}-containing antacid. A normal individual can ingest 20 g per day without developing chronic hypercalcemia, but clinically dangerous hypercalcemia may follow the administration of as little as 3.4 g per day to patients with uremia. Bicarbonate that accompanies the absorption of Ca^{2+} from $CaCO_3$ causes a slight-to-moderate metabolic alkalosis after each dose; a clinically significant and persistent alkalosis develops only slowly during a maintenance regimen.

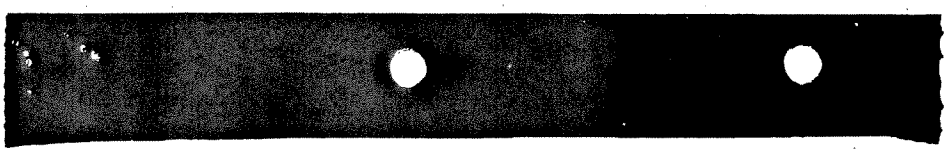
The main route of elimination of absorbed Ca^{2+} is by urinary excretion, which varies with the creatinine clearance. With long-term use of Ca^{2+}-containing antacids, absorption exceeds excretion for many weeks and it may take months to achieve a new steady state (*see* Makoff *et al.*, 1969; *see also* Chapter 62).

Magnesium-Containing Antacids. The chronic ingestion of antacid doses of $Mg(OH)_2$ causes only slight increases in plasma concentrations of Mg^{2+} in persons with normal renal function. Since renal excretion is the principal route of elimination, toxic concentrations may occur in persons with renal failure (*see* Chapter 27).

Adverse Effects. Adverse effects of antacids may be classified into those that are dependent on the magnitude of change in pH or acid–base balance and those that are dependent upon a particular chemical entity.

pH-Dependent Effects. Distortions of acid–base balance by absorbed cations from antacids are usually transient and clinically insignificant in persons with normal renal function. In the past, when large doses of $NaHCO_3$ and/or $CaCO_3$ were commonly administered with milk or cream for the management of peptic ulcer, the milk-alkali syndrome occurred relatively frequently. This syndrome results from the ingestion of large quantities of Ca^{2+} and absorbable alkali; effects consist of hypercalcemia, reduced secretion of parathyroid hormone, retention of phosphate, precipitation of calcium salts in the kidney, and renal insufficiency. In general, alkaluria from the long-term use of any antacid predisposes to nephrolithiasis by favoring precipitation of calcium phosphate.

Composition-Dependent Effects. Antacids affect bowel habits. $Al(OH)_3$ causes constipation in rough proportion to the dose. The effect is greater in elderly patients. The most frequent side effect of $Mg(OH)_2$ is loose stools or diarrhea. With preparations that contain both $Al(OH)_3$ and $Mg(OH)_2$ the net effect depends on the ratio of the two components and the quantity



used; if the dose of $Mg(OH)_2$ is large enough (in excess of 8.5 g per day), diarrhea will prevail. Magnesium trisilicate and $MgCO_3$ also cause laxation. The effects of $CaCO_3$ are variable, but constipation has been reported more frequently than laxation.

The release of CO_2 from carbonate-containing antacids causes belching, abdominal distention, flatulence, and occasional nausea. Bicarbonate is usually neutralized in the stomach or absorbed, such that only belching results. Gastroesophageal reflux may be exacerbated during episodes of belching.

Al^{3+}-containing antacids rarely cause adverse effects in persons with normal renal function, although severe hypophosphatemia can sometimes occur. In persons with renal impairment, long-term administration of Al^{3+} either in medications or as a contaminant of fluids used for dialysis or alimentation can exacerbate or even initiate osteodystrophy, proximal myopathy, and encephalopathy; the latter may take the form of dementia or seizures. Hyperaluminumemia results, in part, from diminished renal clearance of Al^{3+} and may be exacerbated by increased absorption of Al^{3+} as a result of hyperparathyroidism associated with uremia; however, some investigators attribute the hyperparathyroidism to hyperaluminumemia. The osteodystrophy is thought to result in part from deposition of Al^{3+} in bone. The use of Al^{3+}-containing compounds as the major method to decrease intestinal absorption of phosphate in uremic patients seems hazardous and inappropriate. Suitable doses of $CaCO_3$ similarly reduce phosphate absorption and suppress concentrations of phosphate and parathyroid hormone in plasma without causing hypercalcemia (*see* Bournerias *et al.*, 1983; Gokal *et al.*, 1983; Coburn and Salusky, 1989). For reviews of Al^{3+} toxicity, *see* Mayor and Burnatowska-Hledin (1986), Sherrard (1986), Mach and colleagues (1988), and Monteagudo and coworkers (1989).

Knowledge of the Na^+ content of antacids can be important, particularly for patients with heart failure or hypertension who should limit Na^+ intake. Numerous preparations are suitably low in Na^+ (*see* Table 37–2).

Drug Interactions. Chiefly by altering gastric and urinary pH, antacids may alter rates of dissolution and absorption, bioavailability, and renal elimination of a number of drugs. Thus, it is prudent to avoid concurrent use of antacids and drugs intended for systemic absorption (*see* Hurwitz, 1977; Ritschel, 1984). Most interactions can be avoided by taking antacids 2 hours before or after ingestion of other drugs.

The interactions of antacids with other drugs may be complex, in part because the chemical properties and physiological effects of the compounds vary. Compounds containing Al^{3+} delay gastric emptying, thereby slowing the entry of drugs to the absorptive surface of the small intestine and hence the rate of absorption. However, there may be no effect on bioavailability, particularly if additional time for dissolution in the stomach makes later absorption more rapid. Generally, unless bioavailability is also affected, altered rates of absorption have little clinical significance when drugs are given chronically in multiple doses. In combination products, compounds that contain Mg^{2+} can partially offset the effects of Al^{3+} on gastric motility. Magnesium trisilicate and Al^{3+} compounds are notable for their propensity to adsorb drugs and to form insoluble complexes that are not absorbed. Thus, through a combination of factors many antacids decrease the bioavailability of iron, tetracyclines, isoniazid, ethambutol, some antimuscarinic drugs, benzodiazepines, phenothiazines, ranitidine, indomethacin, phenytoin, nitrofurantoin, vitamin A, fluoride, and phosphate. Antacids reportedly decrease the bioavailability of atenolol and propranolol and increase that of metoprolol. Antacids increase the dissolution and absorption of the acidic forms of sulfonamides and the rate of absorption of levodopa.

Alkalinization of the urine affects renal clearance of drugs that are weak acids or bases (*see* Chapter 1). Concurrent antacid therapy increases the rate of elimination of salicylates and phenobarbital and decreases the elimination of amphetamine, ephedrine, mecamylamine, pseudoephedrine, and quinidine.

Antacids decrease the hepatic metabolism of ranitidine and reduce the efficacy of nitrofurantoin in the therapy of urinary tract infections. Thiazide diuretics cause retention of Ca^{2+}, and may thus exacerbate hypercalcemia from $CaCO_3$.

PREPARATIONS AND DOSAGE

Antacid products vary widely in their chemical composition, acid-neutralizing capacity, and Na^+ content. Table 37–2 provides a comparison of the common oral suspensions. Comparable data on solid dosage forms can be found below. In general, the composition and neutralizing capacity of a tablet are close to those of 5 ml of the corresponding oral suspension.

Both dosage forms frequently contain simethicone, a surface-active agent that is included to disperse foam. This effect may be helpful in reducing gastroesophageal reflux, but simethicone does not have antacid or ulcer-healing properties. Some preparations contain alginic acid, which is thought to protect against the irritating effect of HCl during periods of esophageal reflux; it has no beneficial effects in the treatment of ulcers.

Aluminum Compounds. *Aluminum Hydroxide Gel.* As sold in antacids, "aluminum hydroxide" is actually a mixture of $Al(OH)_3$ and aluminum oxide hydrates, often containing some carbonate. Aluminum hydroxide is marketed mostly in combination with $Mg(OH)_2$ (*see* Table 37–2). During storage, $Al(OH)_3$ loses acid neutralizing capacity; the loss from solid dosage forms exceeds that from suspensions.

Table 37–2. COMPOSITION AND NEUTRALIZING CAPACITY OF REPRESENTATIVE PROPRIETARY ANTACID SUSPENSIONS *

PRODUCT	CONTENT (mg/5 ml)					ACID-NEUTRALIZING CAPACITY ‡ (per 5 ml)
	$Al(OH)_3$	$Mg(OH)_2$	$CaCO_3$	Simeth †	Na	
MAALOX TC §	600	300	0	0	0.8	27
MYLANTA-II	400	400	0	40	1.1	25
KUDROX DOUBLE STRENGTH	565	180	0	0	<15	25
GELUSIL-II	400	400	0	30	1.3	24
CAMALOX	225	200	250	0	1.2	18
DI-GEL	200	200	0	20	<5	—
MARBLEN	400 $MgCO_3$ + 520 $CaCO_3$ ‖			0	3	18
ALTERNAGEL	600	0	0	—	<2.5	16
SILAIN-GEL	282	285	0	25	4.4	15
RIOPAN	540 magaldrate ‖			0	<0.1	15
GELUSIL-M §	300	200	0	25	1.2	15
milk of magnesia	0	390	0	0	0.12	14
MAALOX	225	200	0	0	1.4	13
MYLANTA	200	200	0	20	0.7	13
ALUDROX	307	103	0	—	2.3	12
BASALJEL	$Al(OH)CO_3$ equivalent to 400 $Al(OH)_3$ ‖			—	2.9	12
GELUSIL	200	200	0	25	0.7	12
WINGEL	180	160	0	0	—	10
KOLANTYL GEL	150	150	0	0	<5	10
AMPHOJEL	320	0	0	—	<2.3	10
GAVISCON	31.7 $Al(OH)_3$ + 137 $MgCO_3$ + Na alginate ‖			0	13	4

* Many of these preparations are also available in solid dosage forms. Although the composition of these forms is often similar to that of the suspension, there are variations.

† Simeth = simethicone.

‡ In milliequivalents. In some cases, a 60-minute rather than a 15-minute test was performed.

§ TC = therapeutic concentrate; M = medium strength.

‖ Indicated composition is in lieu of $Al(OH)_3$, $Mg(OH)_2$, and/or $CaCO_3$.

Basic Aluminum Carbonate Gel. The chemical composition of this substance is indefinite and is represented by $Al(OH)CO_3$ in Table 37–2. It is marketed as a suspension that contains the equivalent of 400 mg of $Al(OH)_3$ per 5 ml or as tablets or capsules, each of which contains 500 mg.

Dihydroxyaluminum Sodium Carbonate. This product, a combination of $Al(OH)_3$ and $NaHCO_3$, provides the rapid effect of carbonate and the slower, more sustained effect of the dihydroxyaluminum moiety. Each tablet (ROLAIDS ANTACID) contains 334 mg of the compound, including 53 mg of Na^+, and has the capacity to neutralize 7.5 mEq of acid.

Aluminum Phosphate Gel. This compound, marketed as PHOSPHALJEL, has an insignificant capacity to act as an antacid.

Magnesium Compounds. *Magnesium Hydroxide.* The only single-entity preparation of $Mg(OH)_2$ is *milk of magnesia*. $Mg(OH)_2$ is frequently combined with $Al(OH)_3$.

Magaldrate. Magaldrate is a complex hydroxymagnesium aluminate with the approximate formula $[Mg(OH)^+]_4\ [Al_2(OH)_{10}^{4-}] \cdot 2H_2O$. In the presence of HCl, the hydroxymagnesium is relatively rapidly converted to Mg^{2+} and the aluminate to hydrated $Al(OH)_3$; the $Al(OH)_3$ then reacts more slowly to give a sustained antacid effect. Magaldrate (RIOPAN) is available as a suspension and as tablets either to chew or to swallow; each tablet contains 480 mg of magaldrate and not more than 0.1 mg of Na^+, and has an acid-neutralizing capacity of 13.5 mEq.

Sodium Compounds. *Sodium Bicarbonate.* $NaHCO_3$ is available in tablets that contain 325 to 650 mg. One gram neutralizes 12 mEq of acid. For continuous nasogastric irrigation during surgery or in intensive care, a 0.05-N solution may be used.

Sodium Citrate. As an antacid, sodium citrate is used in the form of a 0.3-M solution, which can be made as needed in hospital pharmacies. Modified Shohl's solution (BICITRA) contains citric acid and sodium citrate and has about the same neutralizing capacity.

Calcium Compounds. *Calcium carbonate* is available as a single-entity preparation under a variety of proprietary names (*e.g.*, TUMS). Tablets contain from 350 to 1250 mg and have an acid-neutralizing capacity of approximately 10 mEq per 500-mg tablet.

Antacid Mixtures. Antacids are used in combination to give both immediate and sustained action, to minimize undesirable effects by using a lower dose of each component, and to use one component to antagonize side effects of another (*e.g.*, laxation versus constipation). The most common

combination is that of $Al(OH)_3$ and $Mg(OH)_2$ (*see* Table 37–2). Most preparations are also available as tablets with composition and neutralizing capacities similar to those of 5 ml of the corresponding suspension. Other combinations include $CaCO_3$ and $Mg_2Si_3O_8$.

Dosage. Recent studies of the efficacy of antacids in healing duodenal ulcers have demonstrated a significant placebo effect, the ineffectiveness of very low doses of antacids, and the lack of need for extremely high doses (greater than 1000 mEq per day). A popular dosage regimen is based on the attempt to neutralize the maximum capacity for production of acid by the stomach (*see* Peterson *et al.*, 1977). Thus, antacids are administered 1 and 3 hours after eating and at bedtime, for a total of 1000 mEq of neutralizing capacity per day. This regimen takes advantage of the postprandial delay in gastric emptying and stresses the value of lowering gastric acid as the neutralizing effect of food begins to wane (*see* Lam, 1988; Soll, 1989). However, this scheme provides little nocturnal protection, since antacids are neutralized or removed rapidly from the empty stomach. More recent studies indicate that smaller doses are equally effective (*see* Kumar *et al.*, 1984). A total daily dose of 400 mEq of neutralizing capacity, taken in portions an hour after meals and at bedtime, appears adequate. This regimen is more convenient and should promote improved patient compliance.

Daily doses of antacid as low as 180 mEq of acid-neutralizing capacity may also be effective, suggesting that factors other than simple neutralization may contribute to the healing effects. Nevertheless, more than 1000 mEq per day may be required in the treatment of patients with Zollinger–Ellison syndrome, even in conjunction with antisecretory drugs.

THERAPEUTIC USES

The clinical status of antacids is in a state of flux.

Peptic Ulcer. In the treatment of duodenal ulcers, antacids and the H_2 antagonists generally produce equivalent effects on the incidence of healing after a 4- to 8-week course of therapy and on the frequency of relapse thereafter. Effective daily doses of antacids have ranged from 120 to 1000 mEq (*see* Berstad, 1982b; Ippoliti *et al.*, 1983; Isenberg *et al.*, 1983; Kumar *et al.*, 1984; Lam, 1988; Soll, 1989). Results in the treatment of gastric ulcers have been less consistent, and in some instances antacids have been no more effective than placebo. In addition to simpler dosing schedules, therapeutic regimens using H_2 antagonists usually result in a lower incidence of side effects. Thus, antacids are not the agents of choice for the treatment of peptic ulcer disease. Moreover, continuous use of antacids for prophylaxis is not recommended for the reasons itemized above. However, high doses of antacids may be useful adjuncts in combination with H_2 antagonists or inhibitors of the H^+,K^+-ATPase for the treatment of giant duodenal ulcers and the Zollinger–Ellison syndrome.

Gastroesophageal Reflux. Changes in lifestyle and eating habits are of primary importance in treating this condition. To reduce gastric acidity and hence the acidity of the refluxate, H_2 antagonists or omeprazole are preferred; if the tone of the lower esophageal sphincter is reduced or esophageal peristalsis is impaired, these may be supplemented by pirenzepine or so-called prokinetic agents, such as bethanechol, metoclopramide, or cisapride. Antacids may still be useful adjuncts for this condition, since they neutralize acidic secretions that are not susceptible to H_2 antagonists and they increase the pressure of the lower esophageal sphincter.

The alginate-containing product GAVISCON reportedly decreases acidic reflux and increases esophageal clearance of acid. This compound has no demonstrable effect on lower esophageal sphincter pressure and is not a potent antacid. The alginate component may protect the mucosa and mechanically impair reflux by forming a viscous layer on the surface of the gastric contents. The efficacy of this product in managing gastroesophageal reflux has not been demonstrated unequivocally. Nonetheless, it is widely used in the treatment of mild-to-moderate reflux esophagitis.

Miscellaneous Uses. During anesthesia, coma, cesarean section, or endoscopy, aspiration of gastric contents may occur and cause pneumonitis or pneumonia. Prior neutralization of gastric acid provides some protection. The aim should be to keep the pH above 3.5 (possibly as high as 5, to suppress peptic activity). Antacids may be given just prior to and during the procedure. However, if aspirated, the particulate antacids themselves can cause pulmonary damage, which makes the use of sodium citrate (15 ml of a 0.3 M solution) attractive (*see* Wrobel *et al.*, 1982). Because conventional antimuscarinic drugs decrease the competency of the lower-esophageal sphincter, their use is not advised.

Antacids and H_2 antagonists are both effective in the prophylaxis of stress ulceration and consequent acute upper-gastrointestinal hemorrhage (*see* Schiessel, 1989). The management of upper-gastrointestinal bleeding has been reviewed by Peterson (1989).

MUSCARINIC ANTAGONISTS

Muscarinic cholinergic antagonists can reduce basal secretion of gastric acid by 40 to 50%; stimulated secretion is inhibited to a lesser extent. Selective antagonists of M_1 receptors are as effective as atropine or other nonselective muscarinic antagonists, but they are less likely to produce the adverse effects that are characteristic of cholinergic blockade (*e.g.*, dry mouth, tachycardia). Two such drugs currently in clinical trial in the United States are pirenzepine and telenzepine. These agents have relatively low affinities for M_2 and M_3 receptors (*see* Chapter 8). Since the muscarinic receptors on histamine-containing cells have not been characterized, it is not clear where the M_1 antagonists act.

Nor is it known whether blockade of M_1 receptors on intramural cholinergic neurons will interrupt transmission of vagal impulses. M_1 antagonists may also inhibit the secretion of gastrin, mucous, and HCO_3^-, which is regulated by acetylcholine acting at M_1 receptors.

Although pirenzepine is less effective than cimetidine in reducing acid secretion, it has produced comparable rates of healing of duodenal ulcers in several clinical trials. Used in maintenance dosage, it also appears to equal cimetidine for preventing the recurrence of ulcers. Both pirenzepine and the more potent telenzepine are quite hydrophilic and penetrate the blood–brain barrier poorly (*see* Carmine and Brogden, 1985). The effective dosage of pirenzepine is 50 mg two or three times daily. The pharmacological properties of muscarinic antagonists are described in Chapter 8.

SUCRALFATE

Sucralfate is a complex formed from sucrose octasulfate and polyaluminum hydroxide. Its primary unit may be represented as $C_{12}H_6O_{11}$-$[SO_3^-Al_2(OH)_5^+]_8 \cdot nH_2O$. When the pH is below 4, there is extensive polymerization and cross-linking of sucralfate. The condensed polymer is a very sticky, viscid, yellow-white gel. Continued reaction with acid gradually consumes $Al_2(OH)_5^+$ until some sucrose octasulfate moieties are entirely freed of Al^{3+}. The reaction is very slow and is incomplete during the sojourn of the substance in the stomach. Sucralfate has no practical acid-neutralizing capacity. Even though the pH in the duodenum is well above 4, the gel retains its viscid, demulcent properties. The gel adheres strongly to epithelial cells and to the base of ulcer craters. The affinity for the crater base is much higher than that for the epithelial surface, and it is difficult to wash the gel from the crater. In man, the gel remains adherent to ulcerated epithelium for longer than 6 hours, and it is more adherent to duodenal than to gastric ulcers. This binding to ulcer craters probably represents the main therapeutic action of sucralfate. Antacids and food do not appear to affect the integrity of the adherent gel, but proteins in foodstuffs adsorb to its luminal surface, thus adding an additional layer. The gel interacts very little with mucin. Investigations *in vitro* show that the gel coating on the mucosa is considerably less permeable to H_3O^+ than are mucin and aluminum hydroxide. It has been proposed that sucralfate stimulates the formation of prostaglandins by the gastric mucosa, thereby exerting a "cytoprotective" effect (Ligumsky *et al.*, 1984).

The incidence and severity of side effects from sucralfate are very low; only constipation (2%) and a sense of dry mouth (less than 1%) appear significant, although diarrhea, nausea, gastric distress, rash, pruritus, and dizziness have also been reported. Sherman and coworkers (1983) found that sucralfate lowers concentrations of phosphate in plasma toward normal in uremic patients. The use of sucralfate also results in elevated plasma concentrations of Al^{3+} in uremic patients (*see* Leung *et al.*, 1983). Studies in laboratory animals indicate that sucralfate can adsorb and thereby reduce the bioavailability of a number of drugs, including tetracycline, phenytoin, digoxin, and cimetidine.

Sucralfate (CARAFATE) is available as 1-g tablets. The dosage is one tablet 1 hour before each meal and at bedtime. Treatment should be continued for 4 to 8 weeks unless healing has been proven. Since the preparation is activated by acid, antacids should not be taken for 30 minutes before or after sucralfate.

There have been a number of prospective trials of sucralfate in the treatment of peptic ulcer. In all studies sucralfate has been effective against both duodenal and gastric ulcers. Administration before meals was found to be distinctly more effective than after meals. In several trials in which sucralfate and cimetidine were compared, the percentage of healed ulcers after sucralfate treatment was about the same as that after cimetidine. After remission, continued treatment with sucralfate postpones relapse more effectively than does cimetidine. However, after discontinuation of treatment, relapses occur sooner with sucralfate than with cimetidine. The rate of healing of gastric ulcer is less than for duodenal ulcer. For additional information about sucralfate, *see* Brogden and colleagues (1984) and Symposium (1989a).

BISMUTH COMPOUNDS

Suspensions of various bismuth colloids have long been self-administered by the laity for gastrointestinal upsets. However, their potential utility in the treatment of peptic ulcers has recently come under scrutiny. Although these compounds have no substantial acid-neutralizing capacity, they inhibit the activity of pepsin, increase secretion of mucus, and interact with proteins in the necrotic ulcer crater, presumably forming a barrier to the diffusion of acid. Bismuth colloids also cause detachment of *Campylobacter pylori* from the gastric epithelium with subsequent lysis of the bacteria. The therapeutic importance of this action is uncertain, but a growing body of evidence indicates a relationship between colonization by *C. pylori* and a variety of gastric diseases (*see* Hornick, 1987; Talley and Ormand, 1989).

The available colloids are bismuth subgallate, subnitrate, subcitrate, and subsalicylate (PEPTO-BISMOL). They are not currently approved as treatments for peptic ulcer disease in the United States but are under active investigation. In studies with bismuth subcitrate, four daily doses of one tablet or 5 ml containing 120 mg of the drug (taken before meals and at bedtime) are about as effective as cimetidine for the treatment of gastric and duodenal ulcers. Although relatively little of the colloid is absorbed, plasma concentrations of Bi^{3+} rise with prolonged therapy; the long-term use of other bismuth salts produces higher concentrations of Bi^{3+}, which can cause encephalopathy and osteodystrophy. Other potential problems include darkening of the oral cavity. The results of recent clinical studies

with bismuth colloids appear in several reviews (*see* Baron *et al.*, 1986; Bianchi Porro *et al.*, 1986; Elder, 1986).

PROSTAGLANDINS

Prostaglandins E_2 and I_2, the predominant prostaglandins synthesized by the gastric mucosa, inhibit the secretion of acid and stimulate the secretion of mucus and bicarbonate (*see* Chapters 24 and 26). The ulcerogenic properties of aspirin-like drugs that inhibit the synthesis of prostaglandins suggest a role for these autacoids in normal gastric function. Because the administration of prostaglandins can protect the gastric mucosa of animals against various ulcerogenic insults, a number of slowly metabolized analogs have been developed and tested in man. These include misoprostol, an analog of PGE_1, which has recently been released for general use in the United States (*see* Chapter 24). Clinical studies indicate that misoprostol is about as effective as H_2 antagonists in promoting the healing of duodenal ulcers. Although the drug displays distinct cytoprotective effects in animals, clinical efficacy appears to require doses of misoprostol (200 μg four times daily) that produce marked suppression of acid secretion. By contrast, such doses do not appear to be as effective as H_2 antagonists in healing gastric ulcers or in relieving the symptoms of reflux esophagitis. Current investigation is focused on the use of misoprostol to prevent gastric ulceration in patients who use large doses of aspirin-like drugs for the treatment of arthritis. Although early results have been encouraging, it is not yet clear whether the prophylactic use of misoprostol offers advantages over other therapeutic strategies in such patients.

Effective oral doses of misoprostol and related agents cause diarrhea and some abdominal cramping. Although these side effects are experienced frequently, they are usually self-limiting and rarely interfere with therapy. These compounds are potential abortifacients and should not be used in women in whom conception is a possibility. The actions and therapeutic use of misoprostol have been reviewed by Monk and Clissold (1987) and in Symposia (1988, 1989b).

MISCELLANEOUS DRUGS FOR PEPTIC ULCER DISEASE

A number of other drugs are in use or under investigation as antiulcer agents. Carbenoxolone, a liquorice extract in general use as an antiulcer drug in Europe since 1962, is an oleandane derivative obtained from glycyrrhiza. The drug has a steroid-like structure and possesses significant mineralocorticoid activity. While other mineralocorticoids do not have antiulcer properties, the concurrent administration of spironolactone interferes with the therapeutic effect of carbenoxolone.

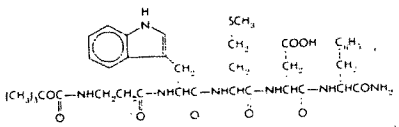
Carbenoxolone alters the composition of mucus and enhances the mucosal barrier to diffusion of acid. Suggested (but unproven) therapeutic effects of carbenoxolone include augmentation of glycoprotein synthesis, inhibition of enzymes that inactivate prostaglandins, and suppression of the activation of pepsinogen. Although in some trials carbenoxolone has appeared to be as effective as cimetidine for peptic ulcers, adverse effects result fairly frequently from its mineralocorticoid actions. These adverse reactions include hypokalemia, fluid retention, and hypertension; impaired glucose tolerance is also observed. These adverse effects constitute major deterrents to the use of carbenoxolone (*see* Barrowman and Pfeiffer, 1982).

Deglycyrrhizinized liquorice is marketed outside the United States as an antiulcer agent. Its actions on the gastroduodenal mucosae are like those of carbenoxolone, but the drug lacks mineralocorticoid activity. Metoclopramide, a prokinetic agent, has been used in the treatment of peptic ulcer with the intention of augmenting normal peristalsis and abolishing the enterogastric reflux of bile, which is thought to be a factor in the pathogenesis of many gastric and some duodenal ulcers. It is of some value in the treatment of gastric ulcer, but its efficacy has been poor in duodenal ulcer. Metoclopramide reduces gastroesophageal reflux and is used in the management of reflux esophagitis; it is discussed in Chapter 38.

PROMOTERS OF GASTRIC SECRETION

To evaluate gastric secretory problems, it may be useful to determine whether parietal cell function is normal. Use of histamine (with an H_1 antagonist), H_2 agonists, or muscarinic agonists is limited by adverse effects. Gastrin and its analogs cause fewer and less severe side effects and are more useful for this purpose.

Pentagastrin. Gastrin, a heptadecapeptide, is a potent physiological gastric secretagogue that is released from the pyloric antrum by vagal stimuli and in response to feeding. Smaller fragments of the peptide are also fully active, and a synthetic pentapeptide, pentagastrin, is available to test gastric function; its structure is as follows:



Pentagastrin

The most prominent action of pentagastrin is to stimulate the secretion of gastric acid, pepsin, and intrinsic factor. It also stimulates pancreatic secretion, inhibits absorption of water and electrolytes from the ileum, relaxes the sphincter of Oddi, and increases blood flow in the gastric mucosa. Although it contracts the smooth muscle of the lower esophageal sphincter and the stomach, pentagastrin delays gastric emptying. The half-life of pentagastrin in the circulation is about 10 minutes.

After subcutaneous injection, pentagastrin elicits reproducible gastric secretory responses comparable to those induced by histamine or betazole. Side effects are usually minor and transient; these may include nausea, borborygmi, the urge to defecate, flushing, tachycardia, faintness, and dizziness. Allergic reactions are rare. Gastric secretion begins within 10 minutes, peaks within 20 to 30 minutes, and lasts about an hour (*see* Baron, 1972).

Pentagastrin (PEPTAVLON) is marketed in ampuls containing 0.25 mg/ml. The diagnostic dose is 6 μg/kg, administered by subcutaneous injection.

Baron, J. H.; Barr, J.; Batten, J.; Sidebotham, R.; and Spencer, J. Acid, pepsin and mucus secretion in patients with gastric and duodenal ulcer before and after colloidal bismuth subcitrate. *Gut*, 1986, *27*, 486–490.

Berstad, A. Antacids and pepsin. *Scand. J. Gastroenterol.*, **1982a**, *17*, Suppl. 75, 13–15.

———. Antacid therapy of duodenal ulcer. Effects of smaller doses. *Ibid.*, **1982b**, *17*, Suppl. 75, 97–99.

Bianchi Porro, G.; Parente, F.; Lazzaroni, M.; and Pace, F. Colloidal bismuth subcitrate and two different dosages of cimetidine in the treatment of resistant duodenal ulcer. *Scand. J. Gastroenterol.*, 1986, *21*, Suppl. 122, 39–41.

Binder, H. J., and Donaldson, R. M., Jr. Effect of cimetidine on intrinsic factor and pepsin secretion in man. *Gastroenterology*, 1978, *74*, 371–375.

Black, J. W.; Duncan, W. A. M.; Durant, C. J.; Ganellin, C. R.; and Parsons, E. M. Definition and antagonism of histamine H_2 receptors. *Nature*, 1972, *236*, 385–390.

Bleehen, S. S., and others. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *Br. J. Dermatol.*, 1987, *117*, 81–88.

Bournerias, F.; Monnier, N.; and Reveillaud, R. J. Risk of orally administered aluminum hydroxide and results of withdrawal. *Proc. Eur. Dial. Transplant Assoc.*, 1983, *20*, 207–212.

Caspary, W. F. Measurement of intragastric potential difference. In, *Antacids in the Eighties*. (Halter, F., ed.) Urban & Schwarzenberg, Munich, 1982, pp. 64–69.

Coburn, J. W., and Salusky, I. B. Control of serum phosphorus in uremia. *N. Engl. J. Med.*, 1989, *320*, 1140–1142.

Elder, J. B. Recent experimental and clinical studies on the pharmacology of colloidal bismuth subcitrate. *Scand. J. Gastroenterol.*, 1986, *21*, Suppl. 122, 14–16.

Gailbraith, R. A., and Michnovicz, J. J. The effects of cimetidine on the oxidative metabolism of estradiol. *N. Engl. J. Med.*, 1989, *321*, 269–274.

Gokal, R.; Ramos, J. M.; Ellis, H. A.; Parkinson, I.; Sweetman, V.; Dewar, J.; Ward, M. K.; and Kerr, D. N. Histological renal osteodystrophy and 25-hydroxycholecalciferol and aluminum levels in patients on continuous ambulatory peritoneal dialysis. *Kidney Int.*, 1983, *23*, 15–21.

Hornick, R. B. Peptic ulcer disease: a bacterial infection? *N. Engl. J. Med.*, 1987, *316*, 1518.

Ippoliti, A.; Elashoff, J.; Valenzuela, J.; Cano, R.; Frankl, H.; Samloff, M.; and Koretz, R. Recurrent ulcer after successful treatment with cimetidine or antacid. *Gastroenterology*, 1983, *85*, 875–880.

Isenberg, J. I.; Peterson, W. L.; Elashoff, J. D.; Sanderfeld, M. A.; Reedy, T. J.; Ippoliti, A. F.; Van Deventer, G. M.; Frankl, H.; Longstreth, G. F.; and Anderson, D. S. Healing of benign gastric ulcer with low-dose antacid or cimetidine: a double-blind, randomized, placebo-controlled trial. *N. Engl. J. Med.*, 1983, *308*, 1319–1324.

Jensen, R. T.; Collen, M. J.; Pandol, S. J.; Allende, H. D.; Raufman, J.-P.; Bissonette, B. M.; Duncan, W. C.; Durgan, P. L.; Gillin, J. C.; and Gardner, J. D. Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N. Engl. J. Med.*, 1983, *308*, 883–887.

Kumar, N.; Vij, J. C.; Karol, A.; and Anand, B. S. Controlled therapeutic trial to determine the optimum dose of antacids in duodenal ulcer. *Gut*, 1984, *25*, 1199–1202.

Leung, A. C.; Henderson, I. S.; Halls, D. J.; and Dobbie, J. W. Aluminum hydroxide versus sucralfate as a phosphate binder in uraemia. *Br. Med. J.*, 1983, *30*, 1379–1381.

Ligumsky, M.; Karmski, F.; and Rochmilewitz, D. Sucralfate stimulation of gastric PGE synthesis: possible mechanism to explain its effective cytoprotective mechanism. *Gastroenterology*, 1984, *86*, 1164.

Lind, T.; Cederberg, C.; Ekenved, G.; Hagland, U.; and Olbe, L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut*, 1983, *24*, 270–276.

Lux, G.; Hartog, C.; Ruppin, H.; and Rösch, W. Combined acid secretion and gastric emptying under antacid and pirenzepine. In, *Antacids in the Eighties*. (Halter, F., ed.) Urban & Schwarzenberg, Munich, 1982, pp. 57–63.

Makoff, D. L.; Gordon, A.; Franklin, A. S.; and Gerstein, A. R. Chronic calcium carbonate therapy in uremia. *Arch. Intern. Med.*, 1969, *123*, 15–21.

Peterson, W. L.; Sturdevant, R. A. L.; Frankl, H. D.; Richardson, C. T.; Isenberg, J. I.; Elashoff, J. D.; Sones, J. Q.; Gross, R. A.; McCallum, R. W.; and Fordtran, J. S. Healing of a duodenal ulcer with antacid regimen. *N. Engl. J. Med.*, 1977, *297*, 341–345.

Sherman, R. A.; Hwang, E. R.; Walker, J. A.; and Eisinger, R. P. Reduction in serum phosphorus due to sucralfate. *Am. J. Gastroenterol.*, 1983, *78*, 210–211.

Walan, A.; Bader, J.; Classen, M.; Lamers, C. B. H. W.; Piper, D. W.; Rutgersson, K.; and Eriksson, S. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N. Engl. J. Med.*, 1989, *320*, 69–75.

Weberg, R., and Berstad, A. Gastrointestinal absorption of aluminum from single doses of aluminum containing antacids in man. *Eur. J. Clin. Invest.*, 1986, *16*, 428–432.

Wrobel, J.; Koh, T. C.; and Saunders, J. M. Sodium citrate: an alternative antacid for prophylaxis against aspiration pneumonitis. *Anaesth. Intensive Care*, 1982, *10*, 116–119.

Monographs and Reviews

Adams, M. H.; Ostrosky, J. D.; and Kirkwood, C. F. Therapeutic evaluation of omeprazole. *Clin. Pharm.*, 1988, *7*, 725–745.

Alfrey, A. C. Aluminum. *Adv. Clin. Chem.*, 1983, *23*, 69–91.

Aymard, J.; Aymard, B.; Netter, P.; Bannwarth, B.; Trechot, P.; and Streiff, F. Haematological adverse effects of histamine H_2-receptor antagonists. *Med. Toxicol. Adverse Drug Exp.*, 1988, *3*, 430–448.

Baron, J. H. Gastric function tests. In, *Chronic Duodenal Ulcer*. (Wastell, C., ed.) Appleton-Century-Crofts, New York, 1972, pp. 82–114.

———. (ed.). *Cimetidine in the 80's*. Churchill Livingstone, Edinburgh, 1981.

Barrowman, J. A., and Pfeiffer, C. J. Carbenoxolone: a critical analysis of its clinical value in peptic ulcer. In, *Drugs and Peptic Ulcer*., Vol. 1. (Pfeiffer, C. J., ed.) CRC Press, Boca Raton, Fla., 1982, pp. 123–132.

Black, J. W., and Shankley, N. P. How does gastrin act to stimulate oxyntic cell secretion? *Trends Pharmacol. Sci.*, 1987, *8*, 486–490.

Brogden, R. N.; Carmine, A. A.; Heel, R. C.; Speight, T. M.; and Avery, G. S. Ranitidine: a review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. *Drugs*, 1982, *24*, 267–303.

Brogden, R. N.; Heel, R. C.; Speight, T. M.; and Avery, G. S. Sucralfate: a review of its pharmacodynamic properties and therapeutic use in peptic ulcer disease. *Drugs*, 1984, *27*, 194–209.

Carmine, A. A., and Brogden, R. N. Pirenzepine: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in peptic ulcer disease and other allied diseases. *Drugs*, 1985, *30*, 85–126.

Clemens, J. D., and Feinstein, A. R. Calcium carbonate and constipation: an historical review of medical mythopoeia. *Gastroenterology*, 1977, *72*, 957–961.

Clissold, S. P., and Campoli-Richards, D. M. Omeprazole; a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger–Ellison syndrome. *Drugs*, 1986, *32*, 15–47.

Forte, J. G.; Hanzel, D. K.; and Urushidani, T. Mechanisms of parietal cell function. In, *Advances in Drug Therapy of Gastrointestinal Ulceration*. (Garner, A., and Whittle, B. J. R., eds.) John Wiley & Sons, Ltd., New York, 1989, pp. 33–52.

Ganellin, C. R., and Parsons, M. E. (eds.). *Pharmacology of Histamine Receptors*. John Wright & Sons, Ltd., Bristol, England, 1982.

Holtermüller, K. H., and Dehdaschti, M. Antacids and hormones. *Scand. J. Gastroenterol.*, 1982, *17*, Suppl. 75, 24–31.

Hurwitz, A. Antacid therapy and drug kinetics. *Clin. Pharmacokinet.*, 1977, *2*, 269–280.

Lam, S. K. Antacids: the past, the present, and the future. *Baillieres Clin. Gastroenterol.*, 1988, *2*, 641–654.

Lindberg, P.; Brandstrom, A.; and Wallmark, B. Structure–activity relationships of omeprazole analogues and their mechanism of action. *Trends Pharmacol. Sci.*, 1987, *8*, 399–402.

Mach, J. R., Jr.; Korchik, W. P.; and Mahowald, M. W. Dialysis dementia. *Clin. Geriatr. Med.*, 1988, *4*, 853–867.

Mayor, G. H., and Burnatowska-Hledin, M. The metabolism of aluminum and aluminum-related encephalopathy. *Semin. Nephrol.*, 1986, *6*, Suppl. 1, 1–4.

Meredith, G. A. *The Ordeal of Richard Feverel*. (1859; revised in 1878.) New American Library of World Literature, New York, 1961, p. 13.

Monk, J. P., and Clissold, S. P. Misoprostol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of peptic ulcer disease. *Drugs*, 1987, *33*, 1–30.

Monteagudo, F. S.; Cassidy, M. J.; and Folb, P. I. Recent developments in aluminum toxicology. *Med. Toxicol. Adverse Drug Exp.*, 1989, *4*, 1–16.

Nazario, M. The hepatic and renal mechanisms of drug interactions with cimetidine. *Drug Intell. Clin. Pharm.*, 1986, *20*, 342–348.

Peterson, W. L. Gastrointestinal bleeding. In, *Gastrointestinal Disease*, 4th ed. (Sleisenger, M. H., and Fordtran, J. S., eds.) W. B. Saunders Co., Philadelphia, 1989, pp. 397–427.

Powell, J. R., and Donn, K. H. Histamine H_2-antagonist drug interactions in perspective: mechanistic concepts and clinical implications. *Am. J. Med.*, 1984, *77*, Suppl. 5B, 57–84.

Riley, A. J., and Salmon, P. R. (eds.). *Ranitidine*. Excerpta Medica, Amsterdam, 1982.

Ritschel, W. A. Antacids. In, *Antacids and Other Drugs in Gastrointestinal Diseases*. Drug Intelligence Publications, Inc., Hamilton, Ill., 1984, pp. 41–124.

Sachs, G.; Carlsson, E.; Londberg, P.; and Wallmark, B. Gastric H^+,K^+-ATPase as therapeutic target. *Annu. Rev. Pharmacol. Toxicol.*, 1988, *28*, 269–284.

Schiessel, R. Stress ulceration and mucosal acid–base balance. In, *Advances in Drug Therapy of Gastrointestinal Ulceration*. (Garner, A., and Whittle, B. J. R., eds.) John Wiley & Sons, Ltd., New York, 1989, pp. 221–230.

Sedman, A. J. Cimetidine—drug interactions. *Am. J. Med.*, 1984, *76*, 109–114.

Sherrard, D. J. Aluminum and renal osteodystrophy. *Semin. Nephrol.*, 1986, *6*, Suppl. 1, 5–11.

Soll, A. H. Duodenal ulcer and drug therapy. In, *Gastrointestinal Disease*, 4th ed. (Sleisenger, M. H., and Fordtran, J. S., eds.) W. B. Saunders Co., Philadelphia, 1989, pp. 814–879.

Ström, M. Antacid side-effects on bowel habits. *Scand. J. Gastroenterol.*, 1982, *17*, Suppl. 75, 54–56.

Symposium. (Various authors.) International Symposium on Gastroenterology. Focus on misoprostol. *Postgrad. Med. J.*, 1988, *64*, Suppl. 1, 1–88.

Symposium. (Various authors.) The 5th International Sucralfate Research Conference. *Am. J. Med.*, 1989a, *86*, 1–152.

Symposium. (Various authors.) Ulcer epidemiology. *Gastroenterology*, 1989b, *96*, Suppl., 559–681.

Talley, N. J., and Ormand, J. E. Is antibacterial therapy against *Campylobacter pylori* useful in the treatment of indigestion and chronic peptic ulceration? *Trends Pharmacol. Sci.*, 1989, *10*, 36–40.

Wolfe, M., and Soll, A. H. The physiology of gastric acid secretion. *N. Engl. J. Med.*, 1988, *319*, 1707–1715.

Zeldis, J. B.; Friedman, L. S.; and Isselbacher, K. J. Drug therapy: ranitidine—a new H_2-receptor antagonist. *N. Engl. J. Med.*, 1983, *309*, 1368–1373.

REVIEWS

Central Nervous System Reactions to Histamine-2 Receptor Blockers

Thomas G. Cantú, PharmD, and Joan S. Korek, PharmD

Purpose: To review the incidence, risk factors, pharmacology, and management of central nervous system reactions to histamine-2 receptor (H_2) blockers.

Data Identification: English-language articles were identified through a search of the MEDLINE and Current Contents databases. Bibliographies of retrieved articles were examined for relevant articles. Case reports submitted to the Food and Drug Administration through 19 September 1989 were obtained.

Study Selection: Studies on the association between central nervous system toxicity (psychosis, agitation, hallucinations, delirium, mental status changes, disorientation, confusion, irritability, obtundation, or hostility) and H_2 blockers were analyzed.

Data Extraction: All data on the incidence of and potential predisposing factors for central nervous system reactions to H_2 blockers were analyzed. Limitations of the data are discussed.

Results of Data Synthesis: Central nervous system toxicities have been associated with all H_2 blockers. These reactions generally occur during the first 2 weeks of therapy and resolve within 3 days of drug withdrawal. The estimated incidence of central nervous system reactions is 0.2% or less in outpatients and 1.6% to 80% in hospitalized patients. Cimetidine is most frequently associated with these reactions; however, no clear evidence exists that one H_2 blocker is more likely than another to cause a reaction. Risk factors for central nervous system reactions have been proposed, but only advanced age has some, albeit limited, data to support it as a risk factor. Studies have only infrequently established causality and there have been difficulties in establishing risk factors for and relative incidences of a phenomenon that occurs infrequently in outpatients and that can be multifactorial in origin.

Conclusions: All H_2 blockers are associated with central nervous system reactions. There is no clear evidence of a higher rate of reactions with one H_2 blocker compared with another.

Annals of Internal Medicine. 1991;114:1027-1034.

From The Johns Hopkins Hospital and the University of Maryland, Baltimore, Maryland. For current author addresses, see end of text.

Histamine-2 receptor (H_2) blockers are among the more commonly prescribed medications in the United States (Table 1). These agents are effective for treating and preventing both gastric and duodenal ulcers and are commonly prescribed for gastroesophageal reflux and stress ulcer prophylaxis in critically ill patients. Although H_2 blockers have wide therapeutic indices, adverse reactions can occur in some patients. Central nervous system reactions (that is, delirium, psychosis, confusion, disorientation, hallucinations, hostility, mental status changes, irritability, obtundation, or agitation) have been associated with H_2 blockers, and their use is of concern in patients perceived to be predisposed to these reactions or in whom assessment of mental status is vital (for example, patients in intensive care units). Clinicians often express concern that one H_2 blocker is more likely than another to cause these reactions or that certain patients are predisposed to H_2-blocker-associated central nervous system reactions and therefore must be treated with alternative agents. Indeed, review articles often cite cimetidine as an agent that causes mental confusion; however, they do not mention other H_2 blockers in this context (1-3), which implies that cimetidine is more likely to cause these reactions than the other agents. What is the evidence to support this view? Do the different H_2 blockers differ in their propensity to cause central nervous system reactions? Have risk factors for these reactions been clearly identified? How should these patients be managed? We review the literature on these reactions and attempt to answer these and other questions on the association between H_2 receptor blockers and central nervous system reactions.

Methods

English-language articles about H_2-blocker-associated central nervous system reactions were identified through the MEDLINE and Current Contents databases. Search terms in the MEDLINE database included histamine H_2 receptor blockaders, famotidine (and its registry number), and textwords such as confusion, delirium, psychosis, mental, psychotic, agitation, irritability, obtundation, central nervous system or CNS, hostility, hallucination, and disorientation. Review articles on the adverse effects of H_2 blockers were examined and bibliographies of retrieved articles were reviewed for additional pertinent articles. Further, all cases of H_2-blocker-associated central nervous system reactions reported to the Food and Drug Administration (FDA) between 1 January 1977 and 19 September 1989 were obtained through the Freedom of Information Act.

All data on the incidence of these reactions and potential predisposing factors were analyzed. Published cases of H_2-blocker-associated central nervous system reactions were assessed for causality using an adverse drug reaction algorithm (4).

Table 1. *Commercially A' 'ble Histamine-2 Receptor Blockers*

Generic Name	Trade Name	Manufacturer	Year Marketed
Cimetidine	Tagamet	Smith Kline & French, Philadelphia, Pennsylvania	1977
Ranitidine	Zantac	Glaxo, Research Triangle Park, North Carolina	1983
Famotidine	Pepcid	Merck Sharp & Dohme, West Point, Pennsylvania	1986
Nizatidine	Axid	Eli Lilly and Company, Indianapolis, Indiana	1988

Results

All H_2 blockers have been associated with central nervous system reactions (Table 2). Seventy-eight cases of H_2-blocker-associated central nervous system disturbances have been reported in the literature: 63 cases occurred with cimetidine (5-48), 13 with ranitidine (13, 47-58), and 2 with famotidine (59). Although we found no case of nizatidine-associated central nervous system toxicity in our literature search, 22 cases of nizatidine-associated reactions have been reported to the FDA.

Causality assessments of the 78 published cases yielded the following: 65 cases were possibly caused by the H_2 blocker (14-55, 59), 7 were probably caused by the drug (10-13, 56-58), and 6 were unlikely to be drug-related (5-9, 27). Patients with reactions considered to be probably related to the H_2 blocker had the following general characteristics: symptom resolution on drug withdrawal, symptom re-emergence on re-initiation of H_2-blocker therapy, and the absence of potentially confounding medical conditions or medications. The 6 patients with reactions considered unlikely to be drug-related were excluded from further analyses.

Clinical Presentation

Central nervous system disturbances were noted within 2 weeks of initiating H_2-blocker therapy in 97% of the published cases. Most reactions were described as confusion or disorientation (45%) or as agitation, hostility, or delirium (22%). Hallucinations were noted in approximately 18% of the patients, obtundation or somnolence in 7%, "mental status changes" in 5%, and psychosis or paranoia in 3%. Most reactions resolved within 3 days of discontinuing H_2-blocker therapy, and all resolved within 7 days.

Incidence in Outpatients

Nine epidemiologic surveys have examined the safety of H_2 blockers in outpatients (Table 3). The studies differed in their patient samples and methods of detecting adverse reactions. The incidence of central nervous system toxicity in these studies was exceedingly low, suggesting that these reactions are rare in the outpatient setting.

Six studies focused on cimetidine-associated adverse reactions. Studies that used insensitive markers for adverse reactions (for example, admitting diagnoses or spontaneous reports) or imprecise patient exposure estimates (sales data), or both, yielded the lowest rates (0 to 0.001%) of central nervous system reactions (60-62). In contrast, prospective studies and rigorously controlled experiences yielded higher reaction rates (0.04% to 0.16%) (63-65).

Das and colleagues (66) also found low rates of central nervous system toxicity in a study that evaluated the relative incidence of medical events (or potential central nervous system reactions) in 21 605 control patients and in 37 252 patients receiving either cimetidine or ranitidine. Histamine-2 receptor blockers were not found to be a risk factor for mental confusion (relative risk, 1.1; 95% CI, 0.8 to 1.6).

Postmarketing studies of ranitidine and famotidine have yielded no cases of central nervous system reactions (67, 68), and no large-scale postmarketing studies of adverse reactions associated with nizatidine have been reported. Although these studies lacked causality assessments and often used insensitive methods for detecting central nervous system reactions, it seems clear that H_2-blocker-associated central nervous system reactions are rarely seen in outpatients. Additionally, controlled studies have found no differences in the rate of central nervous system disturbances when outpatients treated with H_2 blockers are compared with controls (61, 65, 66).

Table 2. *Central Nervous System Reactions to Histamine-2 Receptor (H_2) Blockers*

H_2 Blocker	Reported Cases	FDA Cases*
	n	
Cimetidine	63	814
Ranitidine	13	388
Famotidine	2	72
Nizatidine	0	22

* FDA = Food and Drug Administration.

Risk Factors

Identifying variables that increase the likelihood of H_2-blocker-associated central nervous system reactions has proved to be difficult because of the low occurrence of these reactions in outpatients and the inherent difficulties in establishing causality in hospitalized patients. Potential risk factors are discussed below.

Hospitalization

Studies of hospitalized patients consistently find a higher rate of central nervous system reactions to H_2 blockers than do studies of outpatients (Table 4). Two prospective, uncontrolled surveys of hospitalized patients reported cimetidine-associated central nervous system reaction rates of 1.6% and 1.9% (69, 70). However, if only reactions considered by the investigators to be probably or definitely drug related are included, the reaction rates drop to 0.93% and 0.38%, respectively.

Studies focusing on patients who are in intensive care

units or who are critically ill have found substantially higher rates (6.3% to 80%) of mental status changes in patients receiving cimetidine or famotidine (11, 71, 72). Although 15% to 50% of intensive care unit patients experience mental status changes without H_2-blocker therapy, cimetidine treatment is associated with a significant increase in the incidence of central nervous system dysfunction in these patients (71). Ranitidine- or nizatidine-associated central nervous system dysfunction has not been studied in this population.

Choice of H_2-Blocker Therapy

Case reports offer no insight into the relative incidence of central nervous system reactions with the different H_2 blockers. More case reports of cimetidine-associated central nervous system toxicity have been published compared with the other agents, but cimetidine has also been available longer. Similarly, no evidence for a "selectively" toxic agent has emerged; that is, although some patients have "reacted" to cimetidine but not to ranitidine (10, 32, 33), the reverse has also been noted (49, 56).

Only two comparative studies of H_2-blocker-associated adverse reactions have been reported. In a study of critically ill patients, 1 of 16 patients (6.3%) receiving famitodine and 5 of 26 patients (19.2%) receiving cimetidine experienced central nervous system side effects (72). This small study suggests a higher rate of central nervous system disturbances with cimetidine, but the differences were not statistically significant ($P > 0.02$, the Fisher exact test). Further, the rates of central nervous system disturbances in this study were well within what may be expected in intensive care unit patients not receiving H_2-blocker therapy (71).

In the second study, 20 of 16 920 (0.12%) outpatients receiving full-dose cimetidine therapy (≥ 800 mg/d) experienced mental confusion compared with 38 of 18 126 (0.21%) patients receiving ranitidine at a dosage of at least 300 mg/d. The difference in these rates was statistically significant by chi-square analysis, but the relative risk for reactions in the ranitidine group was not significant (relative risk, 1.6; 95% CI, 0.92 to 2.76). Patients receiving maintenance-dose therapy with ranitidine also had a higher rate of central nervous system reactions (0.20%) compared with patients receiving cimetidine (0.16%), but this was not statistically significant (relative risk, 1.09; CI, 0.40 to 2.93) (66).

Thus, there are few data on the relative incidence of central nervous system disturbances associated with the different H_2 blockers. The available data suggest no differences in the rate of central nervous system reactions in intensive care unit patients receiving cimetidine or famotidine, and no comparative studies have been done on the relative incidence of these reactions in intensive care unit patients receiving ranitidine. Outpatients receiving full-dose ranitidine may be more likely to have central nervous system disturbances than patients receiving cimetidine; however, the exceedingly low incidence of these reactions in outpatients makes any detected differences of questionable clinical importance.

Advanced Age

Fifty-eight percent of the published cases of central nervous system toxicity involved elderly patients. Similarly, 59% of the 956 FDA cases of H_2-blocker-associated central nervous system reactions that noted the patient's age involved patients 60 years of age or more. All central nervous system reactions noted by Kowalsky and colleagues (70) in a multicenter study of cimetidine occurred in elderly patients. However, these anecdotal data have limited utility in determining risk factors. In the only comparative analysis, 3.3% of elderly patients (≥ 70 years of age) receiving intravenous cimetidine had central nervous system reactions compared with 0.7% of patients less than 70 years of age ($P = 0.002$, chi-square) (69). Unfortunately, this study was uncontrolled. Therefore, the data could be interpreted as either supporting advanced age as a risk factor for H_2-blocker-associated central nervous system reactions or as reflecting an increased tendency of the elderly to exhibit central nervous system dysfunction secondary to stress or illness (2).

Table 3. *Outpatient Surveys of Central Nervous System Reactions to Histamine-2 Receptor (H_2) Blockers*

Study (Reference)	Sample	Patients	Reactions
		n	*n*(%)
Porter et al. (60)	Patients < 65 years old receiving cimetidine	8552	1 (0.01)
Colin Jones et al. (61)	Patients receiving cimetidine	9928	0
	Age- and sex-matched controls	9351	0
Davis et al. (62)	Estimated cimetidine population	6.2 million	(0.001)
Gifford et al. (63)	Patients receiving cimetidine	9907	8 (0.08)
Humphries et al. (64)	Patients receiving cimetidine	7911	3 (0.04)
Richter et al. (65)	Patients receiving cimetidine	622	1 (0.16)
	Patients receiving placebo	516	0
Das et al. (66)	Patients receiving H_2 blockers	37 252	2.0*
	Control patients	21 605	1.8*
	Patients receiving full-dose cimetidine	16 920	20 (0.12)
	Patients receiving full-dose ranitidine	18 126	38 (0.21)
	Patients receiving maintenance-dose cimetidine	6332	10 (0.16)
	Patients receiving maintenance-dose ranitidine	3553	7 (0.20)
Inman (67)	Patients receiving ranitidine	9600	0
Saigenji (68)	Patients receiving famotidine	6346	0

* Reactions reported as rate/1000 treatment periods.

Table 4. *Hospital Survey* of Central Nervous System Reactions Associated with Histamine-2 Receptor (H_2) Blockers*

Study (Reference)	Sample	Patients	Reactions
		n	*n*(%)
Schentag et al. (11)	Intensive care unit patients receiving cimetidine	36	6 (16.7)
Porter et al. (69)	Patients receiving intravenous cimetidine	1189	19 (1.6)
Kowalsky et al. (70)	Patients receiving cimetidine	261	5 (1.9)
Cerra et al. (71)	Surgical intensive care unit patients*		
	Normal renal and hepatic function	91	20 (22.0)
	Renal and hepatic dysfunction	35	25 (71.4)†
	Receiving intravenous cimetidine	68	34 (50.0)‡
	Receiving antacids	58	11 (19.0)
	Normal renal and hepatic function		
	Receiving intravenous cimetidine	42	13 (30)
	Receiving antacids	49	7 (15)
	Renal and hepatic dysfunction		
	Receiving intravenous cimetidine	26	21 (80)
	Receiving antacids	9	4 (50)
Welage et al. (72)	Intensive care unit patients		
	Intravenous cimetidine	26	5 (19.2)
	Intravenous famotidine	16	1 (6.3)

* Estimated number of patients (*see* text).
† Significantly higher rate than patients with normal renal and hepatic function ($P < 0.05$, chi-square).
‡ Significantly higher rate than patients receiving antacids ($P < 0.05$, chi-square).

Psychiatric Disorders and Psychotropic Drugs

The potential effects of psychiatric illness on H_2-blocker-associated reactions have not been studied. Only 5 (7%) of the 72 published cases of central nervous system toxicity occurred in patients with a history of psychiatric illness or alcohol abuse, whereas 14 (41%) of the 34 cases in which concomitant medications were noted involved patients who were taking psychotropic medications in addition to H_2 blockers. No data suggest that patients with psychiatric disorders or those taking psychotropic medications are at an increased risk for H_2-blocker-associated central nervous system reactions.

Renal or Hepatic Disease

Two studies have noted the incidence of cimetidine-associated central nervous system reactions in patients with or without organ dysfunction (11, 71). Data from these studies did not suggest an increased incidence of reactions in patients with isolated renal or hepatic disease, but the authors suggest that concomitant liver and renal dysfunction increased the risk for central nervous system reactions. One study was uncontrolled (11) and may therefore reflect an increased rate of mental status changes in patients with renal and hepatic dysfunction independent of cimetidine use. The second study (71) noted mental status changes in 217 surgical intensive care unit patients treated with either cimetidine (n = 124) or antacids (n = 93). However, because this study was nonrandomized, significantly more patients with liver and renal disease were treated with cimetidine (P = 0.008, chi-square), suggesting a treatment allocation bias. Rates of central nervous system reactions were only reported for patients with (n = 35) or without (n = 91) both renal and liver disease. Cimetidine-treated patients had a substantially higher rate of reactions, as did patients with liver and renal disease (71) (Table 4). The relative risk for cimetidine-associated central nervous system toxicity was 2.17 (CI, 0.95 to 4.93) in patients without organ dysfunction and 1.82 (CI, 0.85 to 3.86) in patients with concomitant liver and renal disease. The lower relative risk for central nervous system reactions in patients with organ dysfunction suggests that concomitant liver and renal dysfunction did not increase the risk for cimetidine-associated central nervous system reactions in these patients.

H_2-Blocker Dose and Concentrations

Anecdotal experiences do not support a relation between H_2-blocker dose and central nervous system reactions. Of the 40 published cases in which adequate data were provided on the patient's renal function, 22 (55%) involved doses that were consistent with the manufacturer's recommendations, given the patient's estimated creatinine clearance. Furthermore, central nervous system reactions are not associated with the large doses of cimetidine, ranitidine, or famotidine used in the management of patients with the Zollinger-Ellison syndrome (73-77). Patients experiencing cimetidine overdoses have also been generally free of central nervous system toxicity (78-80). Although central nervous system reactions have resolved after a reduction in H_2-blocker doses in some cases (12, 38, 42, 47), dose reduction has not been a successful strategy in others (10, 47).

Similarly, no clear relation has been detected between H_2-blocker concentrations and central nervous system manifestations. In an uncontrolled study of 36 critically ill patients, trough cimetidine concentrations greater than 4.95 μmol/L were noted in 8 patients, 6 of whom had mental status changes. Although it was suggested that cerebrospinal fluid drug concentrations may also correlate with central nervous system disturbances, only five cerebrospinal fluid samples were available (11). This study, as well as one case report (12), suggests a potential relation between cimetidine concentrations and mental status changes.

In contrast, central nervous system toxicity has been

associated with trough cimetidine concentrations of less than 4.95 μmol/L (12, 45) or peak plasma drug concentrations ranging from 2.77 to 7.92 μmol/L (12, 41). Similarly, the absence of toxicity has been noted with a wide range of cimetidine concentrations (12, 42), and patients experiencing overdoses have been asymptomatic despite acute serum cimetidine concentrations as high as 225.72 μmol/L (78) (Table 5). No clear relation was seen between cimetidine peak or trough concentrations and mental status changes in 124 patients, at least 34 of whom experienced central nervous system reactions. A relation was suggested, however, between mean log trough cimetidine concentrations and mean mental status scores that had been "normalized" for the presence or absence of liver or kidney dysfunction (or both) (71).

Although central nervous system manifestations appear to correlate with cimetidine concentrations in some patients (12), no concentration range has demonstrated predictive value for central nervous system toxicity. No data are available on the potential relation between ranitidine, famotidine, or nizatidine concentrations and central nervous system toxicity.

Pharmacology

The mechanism or mechanisms underlying these reactions are not known. Because the primary pharmacologic action of these drugs is the blockade of H_2 receptors, it is tempting to speculate that central nervous system reactions result from central H_2-receptor blockade. Cimetidine, ranitidine, and famotidine enter the cerebrospinal fluid (11, 12, 81-85) (Table 6); however, the role of histamine in the central nervous system is unclear (86, 87), as are the behavioral correlates of central H_2-receptor blockade.

Histamine has depressant effects on the reticular activating system, but histamine-1 receptor (H_1) blockers appear to be more potent in reversing this depressant effect than do H_2 blockers (88). In an animal model of depression, histamine increased animal immobility, which also suggests a depressant effect. Blockade of H_1 receptors does not alter this depression, but cimetidine significantly reduces this response (89). Conversely, stimulation of H_2 receptors increases foot-shock-associated aggression in mice, and H_2-receptor blockade substantially reduces this increased aggression (90). Clearly, more research is needed to elucidate the role of histamine and the consequences of H_2-receptor blockade in the central nervous system.

Histamine-2 blockers also interact with other central nervous system receptors. For example, cimetidine inhibits muscimol (a GABA [γ-aminobutyric acid]-receptor agonist) binding (inhibitory concentration$_{50}$ = 0.15 μmol/L) and increases flunitrazepam binding (effective concentration$_{50}$ = 1.06 μmol/L) in rat brain. These effects are similar to those noted with GABA, but they do not occur with ranitidine (91). Ranitidine potentiates GABA-evoked twitching of guinea pig ileum, which is blocked by atropine (92). Other in-vitro pharmacologic actions include a reduction in the analgesic effects of enkephalins by cimetidine (93) and the anticholinergic properties of both cimetidine and ranitidine (94, 95).

An anticholinergic component of H_2-blocker-associated central nervous system reactions is supported by the resolution of these reactions in all patients (n = 4) treated with physostigmine (7, 45, 53). In two patients, physostigmine had no effect on agitation or obtundation if H_2-blocker therapy had been discontinued but was effective for treating these symptoms when H_2 blockers were being administered (7, 45).

Finally, clinical reactions such as dizziness, fatigue, and seizures have been associated with the inhibition of drug

Table 5. *Cimetidine Plasma Concentrations and Central Nervous System Toxicity*

Study (Reference)	Patient	Sex, Age	Daily Dose	Plasma Drug Concentration			Confusion
				Peak*	Trough*	Other	
		y	mg	← μmol/L →			
Kimelblatt et al. (12)	1	Female, 56	600		0.99		Yes
			300		0.40		No
			600	7.92	2.38		Yes
			300		0.40		No
Graham (41)	2	Female, 54	800	2.77			Yes
			800	3.17			Yes
Edmonds et al. (42)	3	Male, 72	600			13.98	Yes
			400	6.22			No
			600	4.12			Yes
			600	9.35			No
Brie et al. (43)	4	Male, 43	1200		9.50		Yes
Mogelnicki et al. (45)	5	Male, 60	1200		0.36		Yes
			1200		0.51		Yes
Illingworth et al. (78)	6†	Male, 26	16 000			225.7	No
	7†	Male, 42	98 tablets‡			142.6	No
	8†	Male, 26	5200			146.5	No
	9†	Male, 37	6000			17.8	No
Meredith et al. (80)	10†	Not reported	20 000			181.4	No

* Samples for peak assessments were drawn 1.5 to 2.5 hours after administration of the dose; samples for trough assessments were drawn just before administration of the next dose.
† Overdose cases.
‡ Dose was 98 tablets.

Table 6. *Cerebrospinal Fl (CSF) Concentrations of Histamine-2 Recep (H2) Blockers*

Study (Reference)	H_2 Blocker	Patients	Range of CSF Concentration	Mean CSF/Plasma Ratio
		n	*μmol/L*	
Schentag et al. (11)	Cimetidine	5		0.24
	Patients without toxicity	3	0.59 to 0.91	Not reported
	Patients with toxicity	2	3.17 to 5.54	Not reported
Kimelblatt et al. (12)	Cimetidine	1*	0.91	0.51
Jonsson et al. (81)	Cimetidine	7	0.12 to 0.79	0.07
Schentag et al. (82)	Cimetidine	21	Not reported	Not reported
	Renal or liver disease	8	Not reported	0.28
	No renal or liver disease	7	Not reported	0.18
Walt et al. (83)	Ranitidine	13		
	One oral dose	9	0.003 to 0.045	0.021
	Two oral doses	4	0.060 to 0.089	0.044
Kagevi et al. (84)	Ranitidine	10	0.032 to 0.127	0.091
Kagevi et al. (85)	Famotidine	12	0.0 to 0.056	0.098

* Central nervous system toxicity noted in this patient.

metabolism induced by cimetidine (96-98). Although this mechanism has not been implicated in any published cases of cimetidine-associated central nervous system toxicity, it cannot be excluded as a potential mechanism.

Management

Central nervous system reactions associated with H_2-blocker therapy in outpatients are best managed by withdrawing the offending H_2 antagonist. No pharmacologic interventions are generally necessary, and symptoms should resolve within 1 to 3 days. Although most patients can be switched to a different H_2 blocker without the reappearance of toxicity (10, 32, 33, 49, 56, 59), some may react to more than one agent (13, 47, 48).

In critically ill patients, determining the cause of central nervous system disturbances can pose a difficult challenge. Potential causes include infection, anticholinergic toxicity, hypoxia, and metabolic disturbances (99-101). If a temporal relation is noted between the initiation of H_2-blocker therapy and the onset of central nervous system manifestations, the H_2 blocker should be withdrawn. A brief trial of an antipsychotic agent may be warranted if the patient is extremely agitated (20, 27, 49, 59). Pharmacologic interventions (excluding physostigmine) have been uniformly unsuccessful if the suspected H_2 blocker has not been withdrawn (15, 27, 41, 44, 46). Many patients may tolerate a different H_2 blocker without central nervous system disturbances, but many clinicians choose to avoid further H_2-blocker use in such patients. Other options include sucralfate, antacids, or omeprazole, a proton-pump inhibitor. None of these alternatives has been associated with central nervous system reactions.

Discussion

All the H_2 blockers have been associated with central nervous system reactions such as disorientation, confusion, agitation, or psychosis. Unfortunately, several assumptions regarding these reactions have emerged over the last decade: For example, it is assumed that cimetidine is more likely to cause these reactions than are other H_2 blockers and that factors such as high-dose H_2-blocker therapy or the presence of liver and renal disease are risk factors for H_2-blocker-associated central nervous system toxicity (44, 50, 102). However, a comprehensive, critical review of the literature reveals a lack of data to support these statements. Several factors probably contributed to the development of these beliefs. Such factors include difficulties in establishing causality and the bias created once a drug is linked to an adverse reaction. Further clouding this issue are the inherent problems in establishing risk factors for a phenomenon that is extremely uncommon in outpatients and that can be caused by a wide variety of insults in hospitalized patients.

In the published case reports, cimetidine has been associated with central nervous system reactions more often than have the other H_2 blockers. However, the number of reactions reported for each drug is affected by various factors, such as published reports of similar reactions, the duration of drug availability, and the relative market shares of the drugs (103-106). Additionally, the unintentional biases of clinicians may affect the number of reactions reported and published. For example, because cimetidine has been more commonly associated with central nervous system reactions, clinicians may be more likely to attribute mental status changes to cimetidine than to other H_2 blockers or they may avoid its use in critically ill patients. These inherent biases, combined with the lack of data on the demographics of the patient populations exposed to the drug, render case report data useless in determining the relative incidence of adverse reactions.

Comparative studies of H_2 blockers have failed to detect differences in the incidence of central nervous system reactions among the various agents. However, few trials have examined this issue. Thus, although one cannot rule out differences in the propensity of the H_2 blockers to cause or to be associated with central nervous system reactions, there is no clear evidence of differing propensity among these agents.

Proposed risk factors for H_2-blocker-associated central nervous system reactions have included advanced age, use of concomitant psychotropic medications, high-dose H_2-blocker therapy, pre-existing psychiatric disorders, and the presence of liver and kidney disease (39, 44, 50, 99, 107). None of these variables has been shown to increase the risk for H_2-blocker-associated

central nervous system reactions. A substantially increased incidence of "reactions" was noted in the elderly in an uncontrolled study (69); however, the elderly are known to exhibit central nervous system disturbances more commonly during stress or illness (2). Similarly, concomitant liver and renal dysfunction may predispose patients to mental status changes, but these disease states do not appear to increase the risk for cimetidine-associated central nervous system reactions. Finally, the weight of the evidence suggests that H_2-blocker-associated central nervous system reactions are idiosyncratic and not dose related.

The incidence of H_2-blocker-associated central nervous system reactions in outpatients appears not to differ from that noted in patients not receiving H_2 blockers (61, 65, 66). In contrast, the incidence of "reactions" appears higher in hospitalized patients, ranging from 1.6% to 1.9% (69, 70). Whether this reflects an increased susceptibility to H_2-blocker-associated central nervous system toxicity or an increased incidence of mental status changes in hospitalized patients independent of H_2 blocker use is not clear. Furthermore, hospitalized patients can be monitored more closely for adverse reactions than can outpatients, a factor that could also contribute to the increased rate of reactions detected. Surveys of intensive care unit patients yielded even higher rates of reactions, but establishing causality in such patients can be extremely difficult, given that central nervous system manifestations were noted in 15% to 50% of control patients (71). Although cimetidine may increase the incidence of central nervous system disturbances in intensive care unit patients (71), similar studies with the other H_2 blockers have not been reported.

Causality assessments are critical to the scientific investigation of these reactions. However, most studies of H_2-blocker-associated central nervous system toxicity lacked an appropriate control group, thereby making causal links difficult to establish. Even though an inability to establish causality does not exclude a causal relation, properly controlled trials are required to answer questions about risk factors or relative incidences of reactions.

Requests for Reprints: Thomas G. Cantú, PharmD, Drug Information Service, Department of Pharmacy, Carnegie 180, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21205.

Current Author Addresses: Dr. Cantú: Drug Information Service, Department of Pharmacy, Carnegie 180, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21205.
Dr. Korek: University of Maryland at Baltimore, 20 North Pine Street, Baltimore, MD 21201.

References

1. Pucino F, Beck CL, Seifert RL, Strommen GL, Sheldon PA, Silbergleit IL. Pharmacogeriatrics. Pharmacotherapy. 1985;5:314-26.
2. Lipowsky ZJ. Delirium in the elderly patient. N Engl J Med. 1989;320:578-82.
3. Shamburek RD, Farrar JT. Disorders of the digestive system in the elderly. N Engl J Med. 1990;322:438-43.
4. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. JAMA. 1979; 242:623-32.
5. Robinson TJ, Mulligan TO. Cimetidine and mental confusion [Letter]. Lancet. 1977;2:719.
6. Bacigalupo A, van Lint MT, Marmont AM. Cimetidine-induced coma [Letter]. Lancet. 1978;2:45-6.
7. Jenike MA, Levy JC. Physostigmine reversal of cimetidine-induced delirium and agitation. J Clin Psychopharmacol. 1983;3:43-4.
8. Caspi A, Vorek D. Confusion, disorientation following cimetidine. Hosp Formul. 1980;15:204-5.
9. Van Sweden B, Kamphuisen HA. Cimetidine neurotoxicity. EEG and behavior aspects. Eur Neurol. 1984;23:300-5.
10. Bories P, Michel H, Duclos B, Bernaud JJ, Mirouze J. Use of ranitidine, without mental confusion, in patient with renal failure [Letter]. Lancet. 1980;2:755.
11. Schentag JJ, Cerra FB, Calleri G, DeGlopper E, Rose JQ, Bernhard H. Pharmacokinetic and clinical studies in patients with cimetidine-associated mental confusion. Lancet. 1979;1:177-81.
12. Kimelblatt BJ, Cerra FB, Calleri G, Berg MJ, McMillen MA, Schentag JJ. Dose and serum concentration relationships in cimetidine-associated mental confusion. Gastroenterology. 1980;78: 791-5.
13. Potter HP, Byrne EB, Lebovitz S. Fever after cimetidine and ranitidine. J Clin Gastroenterol. 1986;8:275-6.
14. Nouel O, Bernuau J, Lebar M, Rueff B, Benhamou JP. Cimetidine-induced mental confusion in patients with cirrhosis. Gastroenterology. 1980;79:780.
15. McMillen MA, Ambis D, Siegel JH. Cimetidine and mental confusion [Letter]. N Engl J Med. 1978;298:284-5.
16. Sonnenblick M, Rosin AJ, Weissberg N. Neurological and psychiatric side effects of cimetidine—report of 3 cases with review of the literature. Postgrad Med J. 1982;58:415-8.
17. Cohen N, Modai D, Golik A, Eshkoly M, Theitler J, Scapa E. Cimetidine-related cardiac conduction disturbances and confusion. J Clin Gastroenterol. 1989;11:68-9.
18. Quap CW. Confusion: An adverse reaction to cimetidine therapy. Drug Intell Clin Pharm 1978;12:121.
19. Vickery TR. Cimetidine reaction. Drug Intell Clin Pharm. 1978;12: 242.
20. Adler LE, Sadja L, Wilets G. Cimetidine toxicity manifested as paranoia and hallucinations. Am J Psychiatry. 1980;137:1112-3.
21. Spears JB. Cimetidine and mental confusion [Letter]. Am J Hosp Pharm. 1978;35:1035.
22. Arneson GA. More on toxic psychosis with cimetidine [Letter]. Am J Psychiatry. 1979;136:1348-9.
23. Basavaraju NG, Wolf-Klein G, Silverstone FA, Libow LS. Cimetidine-induced mental confusion in elderly. N Y State Med J. 1980; 80:1287-8.
24. Ng JY, Jones TE, Disney AP, Mathew TH. Prolonged confusion after cimetidine [Letter]. Med J Aust. 1981;12:656-7.
25. Weddington WW Jr, Muelling AE, Moosa HH, Kimball CP, Rowlett RR. Cimetidine toxic reactions masquerading as delirium tremens. JAMA. 1981;245:1058-9.
26. Levine ML. Cimetidine-induced coma in cirrhosis of the liver [Letter]. JAMA. 1978;240:1238.
27. Yudofsky SC, Ahern G, Brockman R. Agitation, disorientation, and hallucinations in patients on cimetidine: a report of three cases and literature review. Gen Hosp Psychiatry. 1980;2:233-6.
28. Gordon C. Differential diagnosis of cimetidine-induced delirium. Psychosomatics. 1981;22:251-2.
29. Niv Y, Zlatkis L, Kosakov K. Cimetidine and encephalopathy [Letter]. Ann Intern Med. 1986;105:977.
30. Klotz SA, Kay BF. Cimetidine and agranulocytosis [Letter]. Ann Intern Med. 1978;88:579-80.
31. Thompson J, Lilly J. Cimetidine-induced cerebral toxicity in children [Letter]. Lancet. 1979;1:725.
32. Pedrazzoli S, Petrin P, Pasquali C, et al. Ranitidine reverses cimetidine-induced mental confusion in a patient with Zollinger-Ellison syndrome [Letter]. Arch Surg. 1983;118:256.
33. Rosse RB. Cimetidine and mental status changes [Letter]. J Clin Psychiatry. 1986;47:99-100.
34. Wood CA, Isaacson ML, Hibbs MT. Cimetidine and mental confusion [Letter]. JAMA. 1978;239:2250-1.
35. Menzies-Gown. Cimetidine and mental confusion [Letter]. Lancet. 1977;2:928.
36. Nelson PG. Cimetidine and mental confusion [Letter]. Lancet. 1977;2:928.
37. Delaney JC, Ravey M. Cimetidine and mental confusion [Letter]. Lancet. 1977;2:512.
38. Grimson TA. Reactions to cimetidine [Letter]. Lancet. 1977;1:858.
39. Agarwal SK. Cimetidine and visual hallucinations [Letter]. JAMA. 1978;240:214.
40. Kinnel HG, Webb A. Confusion associated with cimetidine [Letter]. Br Med J. 1979;2:1438.
41. Graham JR. Psychotic reaction to cimetidine, presumably an idiosyncrasy [Letter]. Med J Aust. 1979;2:491-2.
42. Edmonds ME, Ashford RF, Brenner MK, Saunders A. Cimetidine: does neurotoxicity occur? Report of three cases. J R Soc Med. 1979;72:172-5.
43. Brier KL, Dasta JF, Kidwell GA, Schoenfeld SA, Couri D. Cimetidine and mental confusion. Crit Care Med. 1980;8:760-1.
44. Barnhart CC, Bowden CL. Toxic psychosis with cimetidine. Am J Psychiatry. 1979;136:725-6.
45. Mogelnicki SR, Waller JL, Finlayson DC. Physostigmine reversal of cimetidine-induced mental confusion. JAMA. 1979;241:826-7.
46. Russell WL, Lopez LM. Cimetidine-induced mental status changes:

case report and literature re· Am J Hosp Pharm. 1980;37:1667-71.
47. Davies WA. Mental confusion associated with ranitidine [Letter]. Med J Aust. 1983;2:478.
48. Mani RB, Spellun JS, Frank JH, Laureno R. H_2-receptor blockers and mental confusion. Lancet. 1984;2:98.
49. Hughes JD, Reed WD, Serjeant CS. Mental confusion associated with ranitidine [Letter]. Med J Aust. 1983;2:12-3.
50. Sonnenblick M, Yinnon A. Mental confusion as a side effect of ranitidine [Letter]. Am J Psychiatry. 1986;143:257.
51. Epstein CM. Ranitidine and confusion [Letter]. Lancet. 1984;1: 1071.
52. Mandal SK. Psychiatric side effects of ranitidine. Br J Clin Pract. 1986;40:260.
53. Goff DC, Garber HJ, Jenike MA. Partial resolution of ranitidine-associated delirium with physostigmine: case report. J Clin Psychiatry. 1985;44:400-1.
54. Fennelly ME, Earnshaw G, Soni N. Ranitidine-induced mental confusion [Letter]. Crit Care Med. 1987;15:1165.
55. Martinez-Abad M, Delgado Gomis F, Ferrer JM, Morales-Olivas FJ. Ranitidine-induced confusion with concomitant morphine [Letter]. Drug Intell Clin Pharm. 1988;22:914-5.
56. Silverstone PH. Ranitidine and confusion [Letter]. Lancet. 1984;1: 1071.
57. Price W, Coli L, Brandstetter RD, Gotz VP. Ranitidine-associated hallucinations. Eur J Clin Pharm. 1985;29:375-6.
58. MacDermott AJ, Insole J, Kaufman B. Acute confusional episodes during treatment with ranitidine. Br Med J. 1987;294:1616.
59. Henann NE, Carpenter DU, Janda SM. Famotidine-associated mental confusion in elderly patients. Drug Intell Clin Pharm. 1988;22: 976-8.
60. Porter JB, Jick H, Perera DR, Ylvisaker JT, Hunter JR. Long-term follow-up study of cimetidine. Pharmacotherapy. 1984;4:381-4.
61. Colin Jones DG, Langman MJ, Lawson DH. Postmarketing surveillance of the safety of cimetidine: twelve-month morbidity report. Q J Med. 1985;215:253-68.
62. Davis TG, Pickett DL, Schlosser JH. Evaluation of a wordwide spontaneous reporting system with cimetidine. JAMA. 1980;243: 1912-4.
63. Gifford LM, Aeugle ME, Myerson RM, Tannenbaum PJ. Cimetidine postmarket outpatient surveillance program. Interim report on phase I. JAMA. 1980;243:1532-5.
64. Humphries TJ, Myerson RM, Gifford LM, et al. A unique postmarket outpatient surveillance program of cimetidine: report on phase II and final summary. Am J Gastroenterol. 1984;79:593-6.
65. Richter JM, Colditz GA, Huse DM, Delea TE, Oster G. Cimetidine and adverse reactions: a meta-analysis of randomized clinical trials of short-term therapy. Am J Med. 1989;87:278-84.
66. Das AF, Freston JW, Jacobs J, Fox NA, Morton RE. An evaluation of safety in 37,252 patients treated with cimetidine or ranitidine. Intern Med. 1990;11:3-14.
67. Inman WH. PEM News. 1983;1:1-16.
68. Saigenji K, Fukutomi H, Nakazawa S. Famotidine: postmarketing clinical experience. Scand J Gastroenterol Suppl. 1987;22:134:34-40.
69. Porter JB, Beard K, Walker AM, Lawson DH, Jick H, Kellaway GS. Intensive hospital monitoring study of intravenous cimetidine. Arch Intern Med. 1986;146:2237-9.
70. Kowalsky SF, Andritz MB, Calvert JF, Hamilton RA, Platek TE, Stoll WR. A prospective evaluation of cimetidine drug use. Hosp Pharm. 1989;24:105-8.
71. Cerra FB, Schentag JJ, McMillen M, Karawande SV, Fitzgerald GC, Leising M. Mental status, the intensive care unit and cimetidine. Ann Surg. 1982;196:565-70.
72. Welage LS, Wing PE, Schentag JJ, Williams JS, Root JK, Berlin RG. An evaluation of intravenous famotidine (F) versus cimetidine (C) therapy in the critically ill. Gastroenterology. 1988;94:A491.
73. Bonfils S, Mignon M. Management of Zolliner-Ellison syndrome with gastric antisecretory drugs. Scand J Gastroenterol Suppl. 1988;146:111-20.
74. Jensen RT, Gardner JD, Raufman JP, Pandol SJ, Doppman JL, Collen MJ. Zollinger-Ellison syndrome: current concepts and management. Ann Intern Med. 1983;98:59-75.
75. McCarthy DM. Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. Gastroenterology. 1978;74:453-8.
76. Vinayek R, Howard JM, Maton PN, et al. Famotidine in the therapy of gastric hypersecretory states. Am J Med. 1986;81:49-59.
77. Jensen RT, Collen MJ, McArthur KE, et al. Comparison of the effectiveness of ranitidine and cimetidine in inhibiting acid secretion in patients with gastric hypersecretory states. Am J Med. 1984;77:90-105.
78. Illingworth RN, Tarvie DR. Absence of toxicity in cimetidine overdosage. Br J . 1979;1:453-4.
79. Krenzelok EP, Litovitz T, Lippold KP, McNally CF. Cimetidine toxicity: an assessment of 881 cases. Ann Emerg Med. 1987;16: 1217-21.
80. Meredith TJ, Volans GN. Management of cimetidine overdose [Letter]. Lancet. 1979;2:1367.
81. Jonsson KA, Eriksson SE, Kagevi I, Norlander B, Bodemar G, Walan A. No detectable concentrations of oxmetidine but measurable concentrations of cimetidine in cerebrospinal fluid (CSF) during multiple dose treatment. Br J Clin Pharmacol. 1984;17:781-2.
82. Schentag JJ, Cerra FB, Calleri GM, Leising ME, French MA, Bernhard H. Age, disease, and cimetidine disposition in healthy subjects and chronically ill patients. Clin Pharmacol Ther. 1981; 29:737-43.
83. Walt RP, LaBroody SJ, Avgerinos A, Oehr T, Riley A, Mislewicz JJ. Investigations on the penetration of ranitidine into the cerebrospinal fluid and a comparison of the effects of ranitidine and cimetidine on male sex hormones. Scand J Gastroenterol Suppl. 1981;69:19-23.
84. Kagevi I, Wahlby L. CSF concentrations of ranitidine [Letter]. Lancet. 1985;1:164.
85. Kagevi I, Thorhallsson E, Wahlby L. CSF concentrations of famotidine. Br J Clin Pharmacol. 1987;24:849-50.
86. Schwartz JC. Histamine as a transmitter in brain. Life Sci. 1975; 17:503-18.
87. Schwartz JC, Arrang JM, Garbarg M, Korner M. Properties and roles of the three subclasses of histamine receptors in brain. J Exp Biol. 1986;124:203-24.
88. Sastry BS, Phillis JW. Depression of rat cerebral cortical neurones by H_1 and H_2 histamine receptor agonists. Eur J Pharmacol. 1976; 38:269-73.
89. Nath C, Gulati A, Dhawan KN, Gupta GP. Role of central histaminergic mechanism in behavioral depression (swimming despair) in mice. Life Sci. 1988;42:2413-7.
90. Nath C, Gulati A, Dhawan KN, Gupta GP, Bhargava KP. Evidence for central histaminergic mechanism in foot shock aggression. Psychopharmacol. 1982;76:228-31.
91. Lakoski JM, Aghajanian GK, Gallager DW. Interaction of histamine H_2-receptor antagonists with GABA and benzodiazepine binding sites in the CNS. Eur J Pharmacol. 1983;88:241-5.
92. Trzeciakowski JP, Cole S. Ranitidine potentiates ileum contractions caused by GABA and electrical stimulation. Life Sci. 1986;38:173-82.
93. Takayanagi I, Iwayama Y, Kasuya Y. Narcotic antagonistic action of cimetidine on the guinea-pig ileum. J Pharm Pharmacol. 1978; 30:519-20.
94. Cavanagh RL, Usakewicz JJ, Buyniski JP. A comparison of some of the pharmacological properties of etintidine, a new histamine H_2-receptor antagonist, with those of cimetidine, ranitidine and tiotidine. J Pharmacol Exp Ther. 1983;224:171-9.
95. Re L, Cingolani ML, Concettoni C, Rossini L. Cholinergic effects of cimetidine and ranitidine. Pharmacol Res Commun. 1983;15:485-517.
96. Miller DD, Macklin M. Cimetidine—imipramine interaction: a case report. Am J Psychiatry. 1983;140:351-2.
97. Dalton MJ, Powell JR, Messenheimer JA Jr, Clark J. Cimetidine and carbamazepine: a complex drug interaction. Epilepsia. 1986; 27:553-8.
98. Lofgren RP, Gilbertson RA. Cimetidine and theophylline [Letter]. Ann Intern Med. 1982;96:378.
99. Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry. 1987;144:1218-20.
100. O'Brien JG. Evaluation of acute confusion (delirium). Prim Care. 1990;16:349-60.
101. Hales RE. The diagnosis and treatment of psychiatric disorders in medically ill patients. Milit Med. 1986;151:587-95.
102. McGuigan JE. A consideration of the adverse effects of cimetidine. Gastroenterology. 1981;80:181-92.
103. Carson JL, Strom BL. Techniques of postmarketing surveillance. An overview. Med Toxicol 1986;1:237-246.
104. Griffin JP, Weber JC. Voluntary systems of adverse drug reaction reporting—Part 1. Adverse Drug React Acute Poisoning Rev. 1985; 4:213-30.
105. Strom BL. Overview of different logistical approaches to postmarketing surveillance. J Rheumatol. 1988;15(Suppl 17):9-13.
106. Bateman DN, Chaplin S. Adverse reactions. I. Br Med J. 1988; 296:761-4.
107. Freston JW. Cimetidine. II. Adverse reactions and patterns of use. Ann Intern Med 1982;97:728-734.

THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2000 by Am. Coll. of Gastroenterology
Published by Elsevier Science Inc.

Vol. 95, No. 11, 2000
ISSN 0002-9270/00/$20.00
PII S0002-9270(00)01972-9

Rabeprazole for the Prevention of Pathologic and Symptomatic Relapse of Erosive or Ulcerative Gastroesophageal Reflux Disease

Antonio Caos, M.D., Morry Moskovitz, M.D., Yogeshwar Dayal, M.D., Carlos Perdomo, M.S., Robert Niecestro, Ph.D., Jay Barth, M.D., and the Rabeprazole Study Group

Central Florida Clinical Studies, Ocoee, Florida; Valley Gastroenterology Associates, Beaver, Pennsylvania; New England Medical Center, Boston, Massachusetts; and Eisai Inc., Teaneck, New Jersey

OBJECTIVE: We evaluated the effectiveness and safety profile of 10 and 20 mg of rabeprazole, a new proton pump inhibitor, once daily *versus* placebo in preventing endoscopic and symptomatic relapse for up to 1 yr among patients with healed erosive or ulcerative gastroesophageal reflux disease (GERD).

METHODS: The 52-wk trial used a multicenter, randomized, double-blind, parallel-group design in which 209 men and women were assigned to 10 or 20 mg of rabeprazole once daily in the morning or placebo.

RESULTS: Both rabeprazole doses were significantly superior to placebo in preventing endoscopic relapse ($p < 0.001$), and 20 mg was significantly more effective than 10 mg ($p < 0.04$). Both doses were also significantly superior to placebo in reducing the frequency and severity of heartburn relapse ($p < 0.001$). When adjusted for differences in exposure to study medication, no significant differences were found in the incidence of adverse events. No clinically significant changes were found regarding clinical laboratory parameters, vital signs, electrocardiograms, ophthalmological evaluations, body weight, serum gastrin, and enterochromaffin-like cell histology.

CONCLUSIONS: Once-daily therapy with 10 or 20 mg of rabeprazole effectively prevents pathological and symptomatic GERD relapse. The 20-mg dose is significantly more effective than the 10-mg dose in preventing endoscopic recurrence. Treatment was well tolerated, and no clinically significant safety findings emerged. Our findings support rabeprazole's efficacy in preventing GERD recurrence with excellent tolerability and a short-term favorable safety profile. (Am J Gastroenterol 2000;95:3081–3088. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a frequently occurring condition having potentially important symptomatic and pathological consequences. Prevalence estimates of GERD vary and are hampered by the absence of a precise definition or an accepted gold standard (1). However, in a recent community-based evaluation, approximately 20% of the population reported experiencing weekly heartburn or regurgitation (2).

GERD can include both symptomatic complaints and esophagitis (3). Importantly, GERD is a chronic disorder, and many patients relapse soon after termination of effective therapy (4). Relapse rates range from 50% to 80% within 6 months to 1 yr of discontinuing therapy (5). Thus, effective treatment of patients with GERD requires use of a medication that can prevent relapse while demonstrating favorable safety and tolerability.

Rabeprazole is a newly developed benzimidazole proton pump inhibitor (PPI), which, on a molar basis, has 2- to 10-fold greater antisecretory activity than omeprazole *in vitro* (6–9). The results of controlled clinical trials have demonstrated the effectiveness of rabeprazole therapy in healing patients with erosive or ulcerative GERD (10–13). Such studies have also shown that rabeprazole is well tolerated in a wide range of patients (10–13). We conducted the present study to evaluate the 1-yr effectiveness of rabeprazole in maintaining healing among patients with previously diagnosed erosive or ulcerative GERD. Specifically, we evaluated the effectiveness of 10 and 20 mg of rabeprazole once daily *versus* placebo for the prevention of relapse among patients with previously diagnosed GERD, who were healed at study entry. We also evaluated the effectiveness of the two rabeprazole doses in preventing recurrence of GERD symptoms. Also under investigation were the 1-yr safety and tolerability of 10 and 20 mg of rabeprazole, including its effects on serum gastrin levels and enterochromaffin-like (ECL) cell histology.

MATERIALS AND METHODS

Patients

A total of 209 male and female outpatients >18 yr of age, who met the inclusion and exclusion criteria and provided informed written consent, were enrolled at 27 study sites. To be eligible for enrollment, patients were required to have

Table 1. Demographic Characteristics of Patients Enrolled

Characteristic	Rabeprazole 10 mg qAM (n = 70)	Rabeprazole 20 mg qAM (n = 69)	Placebo qAM (n = 70)	Total (n = 209)	Treatment *p* Value*
Sex					
Male/female	43/27	44/25	39/31	126/83	0.611
Age (year)					
Mean (SD)	58.3(14.8)	57.4(13.6)	55.4(12.9)	57.0(13.8)	0.406
Number of doses of antacid used per day (based on average of last 3 days)					
N	70	68	69	207	
Mean(SD)	0.49(1.16)	1.04(2.89)	0.77(1.47)	0.76(1.99)	0.258
Baseline endoscopy modified Hetzel-Dent esophagitis grade					
N	66	67	70	203†	0.107
Grade 0/1/2†‡	54/12/0	53/14/0	44/26/0	151/52/0	
Baseline GERD heartburn frequency grade					
N	66	67	70	203	0.040
None/few/several/ many/continual	42/13/4/2/5	42/10/7/2/6	32/13/7/3/14	116/36/18/7/25	

* Overall treatment *p* value is adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistic. 0 = Normal mucosa; 1 = no macroscopic erosions, but erythema, hyperemia, or friability present; 2 = superficial ulcerations or erosions involving <10% of surface area of last 5 cm of the esophageal squamous mucosa; 3 = superficial ulceration or erosions involving ≥10%, but <50% of surface area of last 5 cm of the esophageal squamous mucosa; 4 = deep ulceration anywhere in esophagus or confluent erosion of >50% of surface of last 5 cm of esophageal squamous mucosa; 5 = stricture.

† Six patients were not evaluable for efficacy due to study drug misrandomization.

‡ 2+ combines grades 2, 3, 4, and 5.

been diagnosed with erosive or ulcerative GERD and healed as demonstrated by endoscopy within 90 days. Endoscopy requirements at baseline included the absence of active erosions or ulcerations. Women were either not of childbearing potential or were using an approved method of contraception. Potential patients were excluded if they had esophageal ring or stricture or esophagitis secondary to systemic events (*e.g.*, scleroderma or ingested irritants); primary esophageal motility disorders; endoscopic evidence of erosive or ulcerative esophagitis; history of definitive acid-lowering surgery or previous esophageal or gastric surgery (except simple closure of perforation); esophageal or gastric varices; or pyloric stenosis that precluded passage of an endoscope. Patients were also excluded if they were undergoing treatment with anticoagulants, anticholinergics, tricyclic antidepressants, motility agents (*e.g.*, cisapride, metoclopramide), or antineoplastics. Patients with concurrent systemic disorders including renal or hepatic insufficiency were excluded, as were those undergoing treatment for cancer, those with active peptic ulceration or endoscopic evidence of active GI bleeding, those with Zollinger-Ellison syndrome, women who were pregnant or lactating, and individuals with any condition likely to result in poor compliance. Also excluded were patients with clinically significant abnormalities in laboratory test results, those who had received any investigational drug other than rabeprazole within 30 days, those unable to return for scheduled clinic visits, and those who were, in the opinion of the investigator, poor medical or psychiatric risks for therapy with an investigational drug.

Study Design

The trial used a multicenter, randomized, double-blind, parallel-group design and had a duration of 52 wk, in which patients were assigned to treatment with either 10 or 20 mg of rabeprazole once daily or placebo for the prevention of recurrent ulcerative or erosive GERD. Patients were allowed to use nonsteroidal anti-inflammatory drugs, aspirin, or acetaminophen for pain relief. They were also permitted to remain on corticosteroid or nonsteroidal anti-inflammatory drug therapy if appropriate. Patients were provided with antacid (Mylanta), and they were also allowed to take other antacids during the study. Patients were not permitted to take H_2-receptor antagonists, sucralfate, PPIs other than rabeprazole, prostaglandins, anticholinergics, or motility agents.

Study Visits and Efficacy Evaluations

The study consisted of six scheduled visits: baseline, wk 4, wk 13, wk 26, wk 39, and wk 52. At each visit, endoscopic evaluations were performed (except at wk 39, unless clinically indicated at that visit) and graded according to a modified Hetzel-Dent grading scale described in Table 1. Endoscopies were performed by gastroenterologists, who were trained at an investigator's meeting as to the uniform grading of esophagitis findings.

The primary efficacy endpoint was freedom from relapse of erosive or ulcerative GERD. Relapse was defined as a Hetzel-Dent grade 2 or higher at any of the evaluations in patients with a baseline score of 0 or 1. Secondary efficacy endpoints included patients' ratings of heartburn frequency (defined as none, few, several, many, or continual) and severity (graded as none, mild, moderate, severe, or terrible), and number of antacid doses taken during the day. Patients' ratings of the severity of daytime and nighttime heartburn and of antacid use were recorded on a diary card, from which ratings were taken at each clinic visit.

Safety Evaluations

Safety and tolerability were evaluated by recording adverse events (including severity, duration, and outcome), clinical laboratory evaluations, determination of fasting serum gastrin levels, recording of vital signs and body weight (all accomplished at each clinic visit), thyroid function tests (baseline, wk 26, and wk 52), analysis of ECL cell histology (baseline, wk 13, wk 26, and wk 52), ophthalmic examinations, and electrocardiograms (baseline and wk 52).

Specimens (at least four full-thickness mucosal biopsies) for evaluation of ECL cells were taken from the greater curvature of the corpus, approximately 10 cm below the cardia. Specimens were fixed in formalin, embedded in paraffin, sectioned, and stained with either hematoxylin and eosin or a silver impregnation method for the visualization of ECL cells in the oxyntic mucosa. Slides were evaluated for the status of ECL cell proliferation according to the Solcia classification (14, 15). Oxyntic mucosal gastritis was graded as normal, chronic superficial gastritis, chronic interstitial gastritis, or chronic atrophic gastritis. Nonantral endocrine cell hyperplasia was graded as normal, diffuse, linear, micronodular, adenomatoid, dysplasia, or carcinoid. Slides were reviewed in a coded (blinded) fashion.

Statistical Analyses

Demographic and baseline characteristics were summarized for each treatment group, and comparability of the groups was determined by analysis of variance. Analysis of efficacy results was carried out on an intent-to-treat or last-observation-carried-forward basis. Relapse was evaluated using Kaplan-Meier product limit estimates. The response variable in this analysis was the amount of time between randomization and the first occurrence of GERD relapse. The mean and median times to relapse were estimated for each treatment group based on Kaplan-Meier probabilities, and pairwise p values were based on the log rank and Wilcoxon statistics from the PROC LIFETEST (SAS® Version 6.12, Cary, NC). Differences between treatment groups in these and all other tests were considered significant at $p \leq 0.05$.

Between-group differences for all secondary endpoints, including frequency and severity of daytime and nighttime heartburn and average number of antacid doses, were analyzed using Cochran-Mantel-Haenszel and analysis of covariance techniques. These methods were also used to evaluate between-group differences in clinical laboratory values, and the Cochran-Mantel-Haenszel test was also used to compare histological results of the gastric mucosa evaluations in the three treatment groups.

Between-group differences in adverse events rates were analyzed using log rank and Wilcoxon statistics from PROC LIFETEST, as well as the χ^2 statistic for comparison of numbers of patients with laboratory values outside the normal range. Analysis of covariance methods were also used for evaluation of between-group differences in thyroid function tests, vital signs, body weight, electrocardiographic results, and fasting serum gastrin levels.

RESULTS

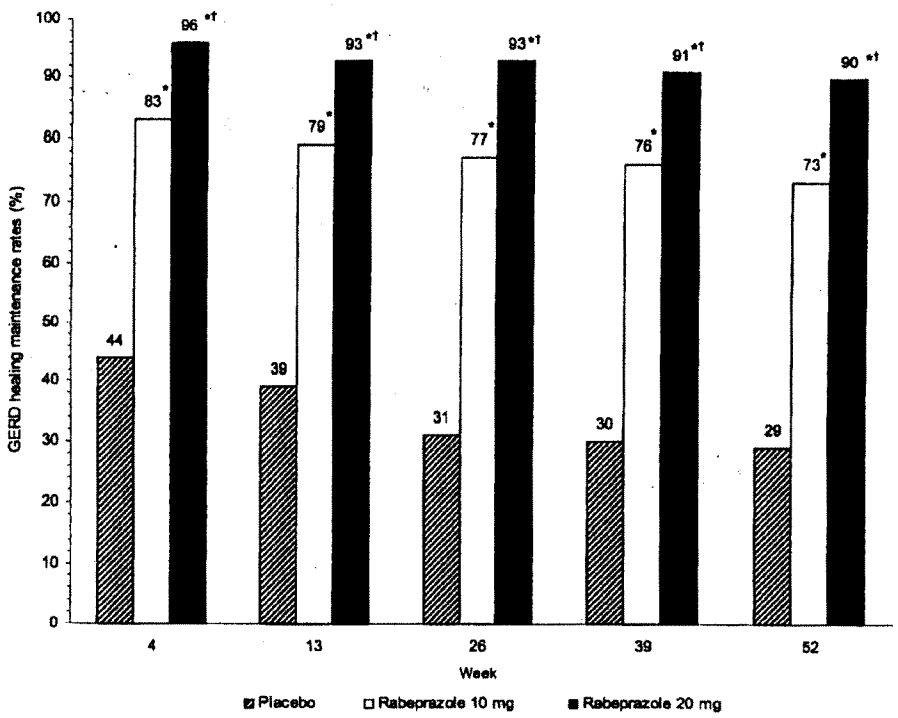
Demographics

Among 209 patients enrolled at 27 US study sites, 70 patients were randomized to 10 mg of rabeprazole, 69 to 20 mg of rabeprazole, and 70 to placebo once daily. The demographic and clinical characteristics for all patients enrolled are summarized in Table 1. No significant differences were found among groups with respect to any demographic or clinical characteristic except baseline GERD heartburn frequency grade. This was higher among patients assigned to placebo than among those randomized to rabeprazole ($p = 0.040$).

Baseline endoscopic data, before initial healing, are available for 73 study participants who were rolled over from a GERD healing study for entry into the healing maintenance study. The majority of these participants had modified Hetzel-Dent esophagitis grades 2 (55%) or 3 (38%) before initial healing, a smaller percentage had grade 4 esophagitis (7%), and none had grades 0, 1, or 5 esophagitis. No information is available regarding endoscopic findings before healing of the other study participants. However, all met the eligibility criteria of having been previously diagnosed with erosive GERD and having no active erosions or ulcerations seen on endoscopy within 90 days of enrollment into the healing maintenance study.

Study Population

The first patient was enrolled on February 13, 1995, and the final patient visit was on October 18, 1996. The number of patients who completed the study was 108 (52%), including 40 patients (57%) who received 10 mg of rabeprazole, 53 patients (77%) treated with 20 mg of rabeprazole, and 15 patients (21%) assigned to placebo ($p < 0.001$ for comparisons between both rabeprazole groups and placebo). The significant difference in completion rates between active treatment and placebo groups was mainly attributable to the large number of placebo patients who discontinued prematurely as a result of a lack of efficacy (66% for placebo *vs* 20% for 10 mg of rabeprazole and 7% for 20 mg of rabeprazole). Among those discontinuing because of a lack of efficacy, the most common reason was clinical relapse (51% for placebo *vs* 17% for 10 mg of rabeprazole and 7% for 20 mg of rabeprazole). The discontinuation rate for patients assigned to 20 mg of rabeprazole was also significantly lower than that for patients assigned to 10 mg of rabeprazole ($p = 0.013$). Differences in study discontinuation rates also led to differences among groups with regard to treatment exposure. The mean duration of exposure was significantly shorter ($p < 0.001$) among patients assigned to placebo (120 days) than among those assigned to 10 mg (249 days) or 20 mg (309 days) of rabeprazole. The mean duration of exposure was also significantly shorter among the 10-mg rabeprazole patients compared to the 20-mg rabeprazole patients ($p = 0.009$).



* $p < 0.001$ compared to placebo.
† $p < 0.04$ compared to rabeprazole 10 mg.

Figure 1. Gastroesophageal reflux disease healing maintenance rates for patients treated with 10 or 20 mg of rabeprazole or placebo (intent-to-treat population).

Endoscopic GERD Relapse

Both doses of rabeprazole were significantly superior to placebo in preventing endoscopic GERD relapse at all time points (Fig. 1) ($p < 0.001$ for all comparisons to placebo for all rabeprazole doses). Relapse rates for the patients receiving 20 mg of rabeprazole were also significantly lower than for those treated with 10 mg of rabeprazole at all time points ($p < 0.04$).

Results of the Kaplan-Meier analysis (Fig. 2) also indicated that both rabeprazole doses were significantly superior to placebo in preventing GERD relapse over the 52-wk study ($p < 0.0001$ for both rabeprazole doses compared to placebo). The 20-mg dose was also significantly superior to 10 mg in maintaining healing ($p = 0.016$). At day 365, the probability of remaining healed was 88% for patients assigned to 20 mg of rabeprazole, 70% for patients assigned to 10 mg of rabeprazole, and 24% for patients randomized to placebo. The mean times to relapse for patients assigned to 20 mg of rabeprazole, 10 mg of rabeprazole, and placebo were 339 days, 286 days, and 133 days, respectively.

Heartburn Frequency and Severity

Both rabeprazole doses were also significantly superior to placebo in reducing rate of heartburn at each time point (Fig. 3) ($p < 0.001$ for all comparisons between rabeprazole and placebo). No statistically significant differences between relapse rates were found among patients assigned to 10 or 20 mg of rabeprazole. Kaplan-Meier analysis indicated that the probability of remaining free of relapse until endpoint was 72% for patients assigned to 20 mg of rabeprazole, 64% for patients randomized to 10 mg of rabeprazole, and 12% for patients assigned to placebo ($p < 0.0001$ for both rabeprazole doses compared to placebo). The difference between the two rabeprazole dosages was not significant.

Both rabeprazole doses were significantly superior to placebo in reducing the severity of relapse of daytime and nighttime heartburn at all time points (Fig. 4) ($p \leq 0.006$ for both rabeprazole doses compared to placebo). Kaplan-Meier analysis indicated probabilities at nearly 41 wk of remaining free from severe daytime heartburn of 91%, 90%, and 46% for 20 mg of rabeprazole, 10 mg of rabeprazole, and placebo ($p < 0.0001$ for both rabeprazole doses *vs* placebo). The respective values for remaining free from severe nighttime heartburn were 91%, 82%, and 39% ($p < 0.0001$ for both rabeprazole doses *vs* placebo).

Antacid Use

Antacid use at each time point (analyzed as change from baseline) was significantly lower for patients in both rabeprazole groups than for patients assigned to placebo (all

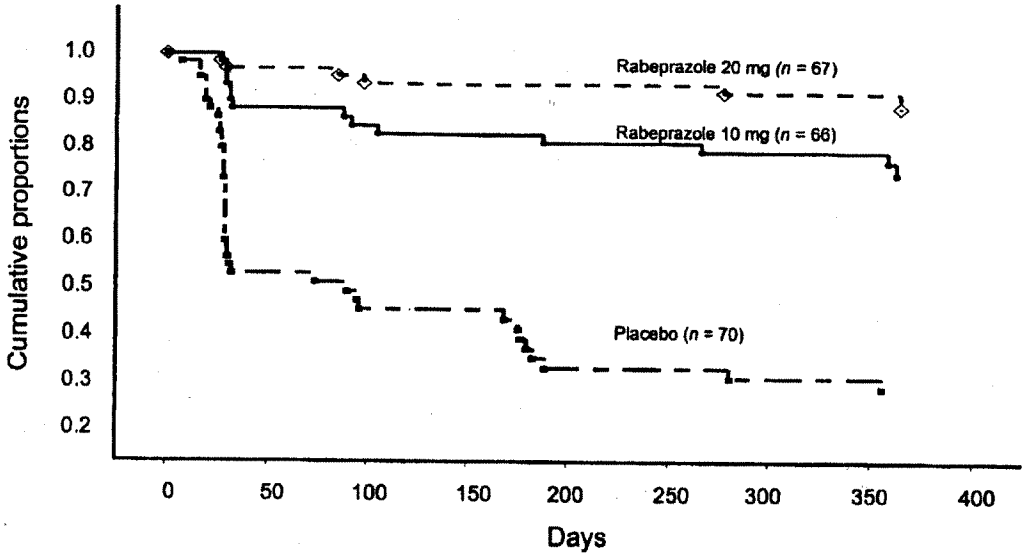
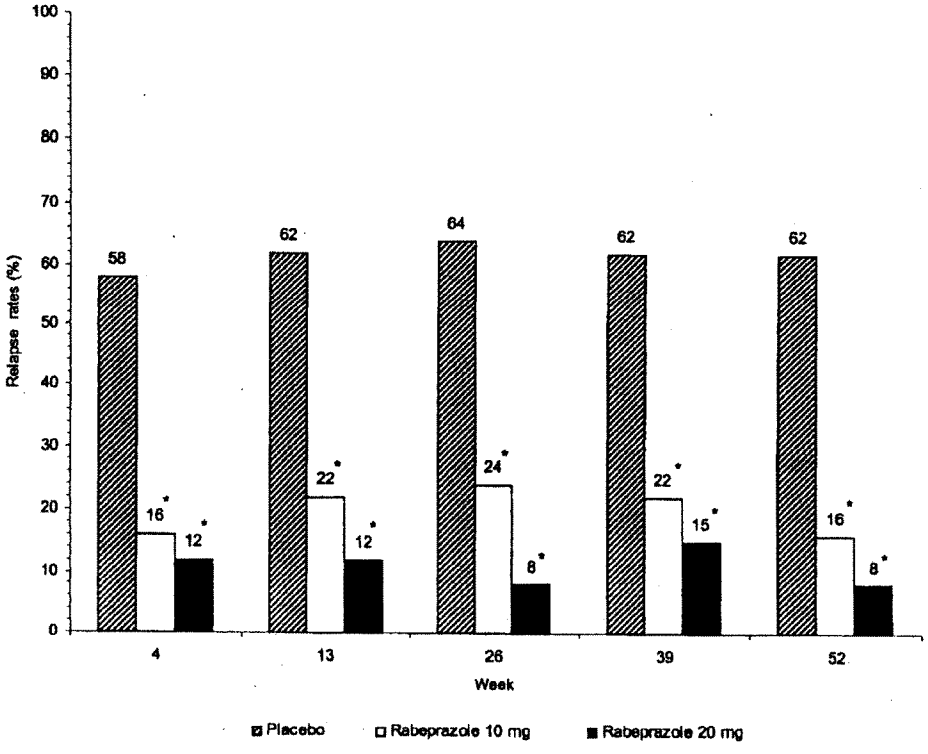
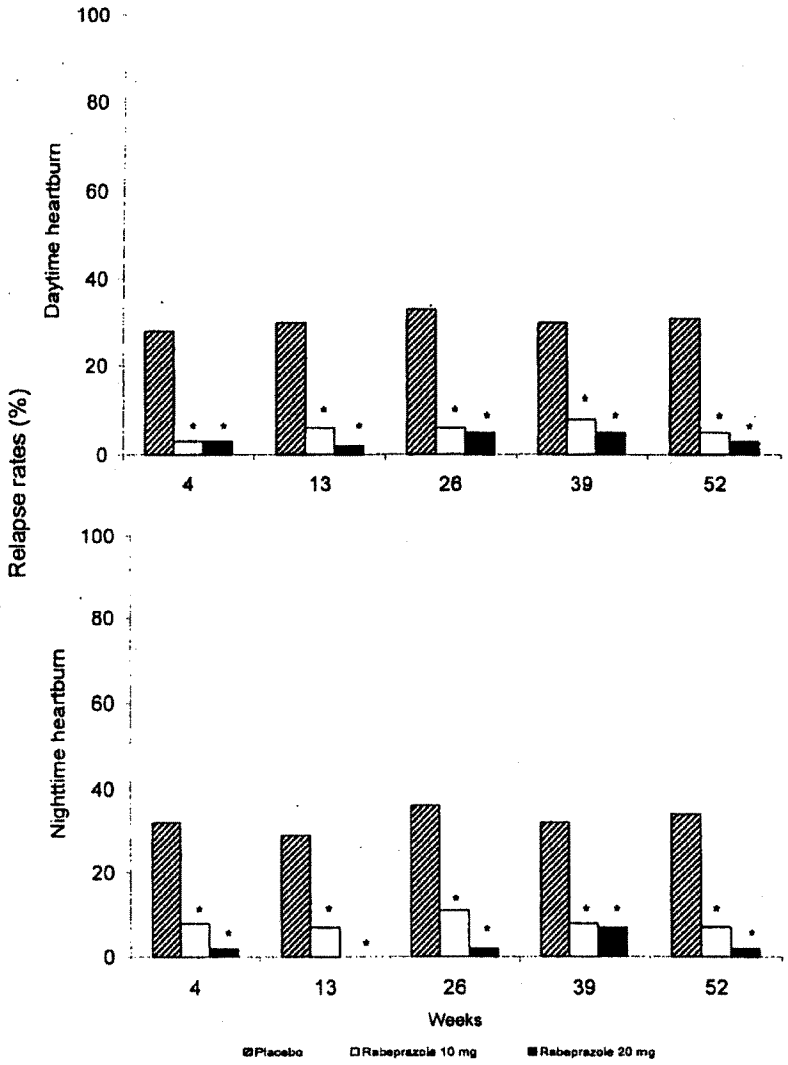


Figure 2. Cumulative proportion of patients in each treatment group who remained free of gastroesophageal reflux disease relapse. $p < 0.0001$ for all comparisons between rabeprazole and placebo (intent-to-treat population).



* $p < 0.001$ compared to placebo.

Figure 3. Heartburn relapse rates for patients treated with 10 or 20 mg of rabeprazole or placebo (intent-to-treat population).



* $p < 0.006$ compared to placebo.

Figure 4. Relapse rates for severe daytime and nighttime heartburn in patients treated with 10 or 20 mg of rabeprazole or placebo (intent-to-treat population).

$p < 0.001$). Mean reductions in antacid use for patients assigned to 20 mg of rabeprazole ranged from −0.24 to −0.65 doses per day. The respective values for patients randomized to 10 mg of rabeprazole were −0.10 to −0.46, and the increases for patients assigned to placebo were 0.59 to 0.80.

Safety and Tolerability

Both rabeprazole doses were well tolerated. Adverse events experienced by at least 10% of patients assigned to either rabeprazole dose are summarized in Table 2. The data in the table show that adverse events occurred significantly more often ($p = 0.008$) among patients assigned to rabeprazole (83% for each dose) than among those assigned to placebo (61%). However, this difference disappeared once adverse events frequency rates were adjusted, using the Kaplan-Meier survival method, to account for significant differences in exposure among placebo patients compared to those receiving active treatment ($p < 0.001$). The most common adverse events reported among patients assigned to rabeprazole were diarrhea, headache, and rhinitis.

No clinically significant changes in hematology, blood chemistry, urinalysis, thyroid function, vital signs, electrocardiograms, ophthalmological evaluations, or body weights occurred during the study.

Serum Gastrin Levels

The mean fasting serum gastrin level decreased by 20.6 pg/ml from baseline in patients receiving 10 mg of rabepra-

Table 2. Adverse Events Experienced by ≥10% of Patients

	Rabeprazole 10 mg qAM (n = 70)	Rabeprazole 20 mg qAM (n = 69)	Placebo qAm (n = 70)
Patients with at least one event	83%	83%	61%
Abdominal pain	10%	10%	3%
Headache	20%	16%	13%
Infection	11%*	3%	1%
Pain	13%*	4%	1%
Surgical procedure	6%	10%*	1%
Diarrhea	26%*	19%	11%
Nausea	11%	9%	6%
Pharyngitis	10%	13%	11%
Rhinitis	16%	17%*	6%

* $p < 0.05$ compared to placebo; no significant differences found when adverse events incidence was adjusted for differences in exposure using Kaplan-Meier survival method.

zole, increased by 1.8 pg/ml in patients receiving 20 mg of rabeprazole ($p = 0.001$, for 20 mg of rabeprazole compared to placebo), and decreased by 31.2 pg/ml in patients treated with placebo. Thirty-nine percent of patients who received 10 mg of rabeprazole and 64% of those receiving 20 mg of rabeprazole experienced hypergastrinemia (serum gastrin >100 pg/ml), compared to 16% for placebo ($p < 0.004$ for both doses compared to placebo).

ECL Cell Histology

No significant differences were found among treatment group with respect to ECL cell histology at baseline. A slight, but statistically significant ($p = 0.019$), difference was detected between the 20-mg rabeprazole and placebo groups at endpoint; 9% of patients receiving 20 mg of rabeprazole had diffuse hyperplasia, and 4% had micronodular hyperplasia *versus* 0% for each category among patients receiving placebo. No patients in any group experienced adenomatoid, dysplastic, or neoplastic changes.

Oxyntic Mucosa Gastritis

Most patients in the 10- and 20-mg treatment groups who were free of superficial or interstitial chronic inflammation at baseline (first adequate sample) remained free of oxyntic mucosal gastritis at endpoint (last adequate sample). There were no significant differences between active treatment and placebo groups. Most cases of inflammation were graded mild to moderate. One case of corpus atrophy developed in the 20-mg group; this was graded as mild.

DISCUSSION

The aim of this study was to determine whether 1 yr of treatment with rabeprazole, a new PPI, would prevent relapse of erosive or ulcerative GERD in recently healed patients. The results indicate that both 10- and 20-mg doses of rabeprazole, once daily in the morning, are significantly superior to placebo in maintaining endoscopic healing among patients with previously diagnosed erosive or ulcerative GERD. Furthermore, both doses are effective in reducing the rate and severity of heartburn recurrence and have a short-term favorable safety profile associated with only modest changes in ECL cell histology.

These results are entirely consistent with previous findings for rabeprazole showing superior healing rates and symptom relief among patients with erosive or ulcerative GERD in comparison to placebo (11), to ranitidine (12), and to omeprazole (13). With regard to the prevention of GERD relapse, other PPIs have demonstrated effectiveness (16, 17), and, recently, in another randomized, double-blind, placebo-controlled clinical trial (18), 10- and 20-mg doses of rabeprazole for up to 1 yr were significantly better than placebo in preventing endoscopic and symptomatic relapse of healed, erosive GERD.

In the present study, we also demonstrate a short-term favorable safety profile for rabeprazole, consistent with previous findings in patients with GERD or gastric or duodenal ulcers (10, 11). As expected from findings for H_2-receptor antagonists and other PPIs (16, 17, 19), rabeprazole significantly increased serum gastrin levels. However, hypergastrinemia related to extended PPI treatment has not been determined to be of clinical significance (20). Rabeprazole for up to 1 yr in the present study also resulted in modest changes in ECL cell scores. An earlier analysis of biopsies from patients receiving 10 or 20 mg of rabeprazole or 10 mg of omeprazole once daily for 1 yr indicated no changes in ECL cell histology from baseline to endpoint (21). These findings are consistent with the conclusion that only minimal and self-limiting nondysplastic and nonneoplastic changes, having little clinical significance, are seen in gastric endocrine cells after long-term once-daily PPI treatment (20).

In this study, there were no statistically significant shifts between baseline and endpoint in the percentage of patients with corpus inflammation or corpus atropy. Only one case of corpus atrophy, graded as mild, was reported after active treatment.

Rabeprazole also did not significantly alter thyroid function, consistent with results from a previous, more extensive safety study showing no significant effects on triiodothyronine, thyroxine, thyroid-stimulating hormone, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, supplemental thyroid hormone, dihydroepiandrosterone, testosterone, cortisol-binding globulin, estrogen, or corticotropin-stimulated cortisol secretion (22). Omeprazole has been shown to inhibit adrenocortical steroidogenesis (23).

In summary, our results demonstrate that once-daily maintenance therapy with 10 or 20 mg of rabeprazole is highly effective in maintaining healing and symptom relief of GERD for 1 yr. The 20-mg dose was significantly superior to the 10-mg dose in healing, and both doses were significantly superior to placebo. One-yr treatment with rabeprazole also proved to be highly tolerable. Observed

changes in serum gastrin levels and ECL cell histology were as expected and entirely consistent with findings for other PPIs.

ACKNOWLEDGMENTS

This work was supported by Eisai Inc., Teaneck, New Jersey. The following investigators participated in the study: Richard Aaronson, M.D. (Chicago Heights, IL), Richard Baerg, M.D. (Tacoma, WA), David Ballard, M.D. (Cincinnati, OH), Tom Bianchi, M.D. (Tallassee, AL), Philip Bird, M.D. (Norman, OK), William Bray, M.D. (Charlotte, NC), Jacques Caldwell, M.D. (Daytona Beach, FL), Antonio Caos, M.D. (Ocoee, FL), Charles L. Colip, M.D. (Portland, OR), Theodore Durbin, M.D. (Long Beach, CA), Norman Gitlin, M.D. (Atlanta, GA), Vernon G. K. Hee, M.D. (Vancouver, WA), Jeffrey Kaine, M.D. (Sarasota, FL), Daniel Kruss, M.D. (Oak Park, IL), Arthur McCullough, M.D. (Cleveland, OH), Morry Moskovitz, M.D. (Beaver, PA), Howard Offenburg, M.D. (Gainesville, FL), Daniel Pambianco, M.D. (Charlottesville, VA), Dennis Riff, M.D. (Anaheim, CA), Walter M. Roufail, M.D. (Winston-Salem, NC), Shariar Safavi, M.D. (Irving, TX), Howard Schwartz, M.D. (Miami, FL), David Scott, M.D. (Shreveport, LA), Stephen Sontag, M.D. (Hines, IL), Z. Vlahcevic, M.D. (Richmond, VA), Richard White, M.D. (Sacramento, CA), Lawrence D. Wruble, M.D. (Memphis, TN).

Reprint requests and correspondence: Jay Barth, M.D., Eisai Inc., Glenpointe Centre West, 500 Frank W. Burr Blvd., Teaneck, NJ 07666.

Received July 9, 1999; accepted June 5, 2000.

REFERENCES

1. Petersen H. The prevalence of gastro-oesophageal reflux disease. Scand J Gastroenterol 1995;30(suppl 211):5–6.
2. Locke GR III, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: A population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112:1448–56.
3. Wienbeck M, Barnert J. Epidemiology of reflux disease and reflux esophagitis. Scand J Gastroenterol 1989;24(suppl 156): 7–13.
4. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988;95:903–12.
5. Olbe L, Lundell L. Medical treatment of reflux esophagitis. Hepatogastroenterology 1992;39:322–4.
6. Morii M, Takata H, Fujisaki H, et al. The potency of substituted benzimidazoles such as E3810, omeprazole, Ro 18–5364 to inhibit gastric H^+, K^+, -ATPase is correlated with the rate of acid-activation of the inhibitor. Biochem Pharmacol 1990; 39:661–7.
7. Fujisaki H, Murakami M, Fujimoto M, et al. The activity of isolated porcine H^+, K^+, -ATPase is inhibited by E3810 (2-[{4-(3-methoxypropoxy)-3-methylpyridin-2-yl}-methylsulfinyl]-1H-benzimidazole, sodium). FASEB J 1990;4:473 (abstract).
8. Oketani K, Murakami M, Fujimoto M, et al. The secretion of acid from isolated rabbit gastric glands is inhibited by E3810 (2-[{4-(3-methoxypropoxy)-3-methylpyridin-2-yl}-methylsulfinyl]-1H-benzimidazole, sodium). FASEB J 1990;4:473 (abstract).
9. Shibata H, Murakami M, Fujimoto M, et al. Histamine-stimulated gastric acid secretion is inhibited in gastric fistula dogs treated with E3810 (2-[{4-(3-methoxypropoxy)-3-methylpyridin-2-yl}-methylsulfinyl]-1H-benzimidazole, sodium). FASEB J 1990;4:473 (abstract).
10. Prakash A, Faulds D. Rabeprazole. Drugs 1998;55:261–7.
11. Cloud ML, Enas N, Humphries TJ, et al. Rabeprazole in treatment of acid peptic diseases: Results of three placebo-controlled dose-response clinical trials in duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease (GERD). Dig Dis Sci 1998;43:993–1000.
12. Humphries TJ, Spera A, Breiter J, et al. Rabeprazole sodium (E3810) once daily is superior to ranitidine 150 mg QID in the healing of erosive or ulcerative gastroesophageal reflux disease. Gastroenterology 1996;110:A139 (abstract).
13. Dekkers CPM, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1999;13:49–57.
14. Dayal Y. Recognition and the histopathologic classification of ECL cell proliferations. Yale J Biol Med 1998;71:257–72.
15. Solcia E, Bordi C, Creutzfeldt W, et al. Histopathological classification of nonantral gastric endocrine growths in man. Digestion 1988;41:185–200.
16. McTavish D, Buckley MM-T, Heel RC. Omeprazole: An updated review of its pharmacology and therapeutic use in acid-related disorders. Drugs 1991;42:138–70.
17. Langtry HD, Wilde MI. Lansoprazole: An update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. Drugs 1997;54:473–500.
18. Birbara C, Breiter J, Perdomo C, et al. Rabeprazole for the prevention of recurrent erosive or ulcerative gastroesophageal reflux disease. Eur J Gastro & Hepatol 2000;12:889–97.
19. Gough AL, Long RG, Cooper BT, et al. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. Aliment Pharmacol Ther 1996;10:529–39.
20. Freston JW. Long-term acid control and proton pump inhibitors: Interactions and safety issues in perspective. Am J Gastroenterol 1997;92:51S-7S.
21. Rindi G, Fiocca R, Humphries T. Argyrophil ECL histology in the gastric corpus and antrum in 243 patients taking rabeprazole 10 mg or 20 mg or omeprazole 20 mg for one year. Digestion 1998;59(suppl 3):234 (abstract).
22. Dammann HG, Burkhardt F, Bell NE, et al. Rabeprazole does not affect endocrine function in healthy subjects. Am J Gastroenterol 1996;91:1909 (abstract 646).
23. Dowie LJ, Smith JE, MacGilchrist AJ, et al. In vivo and in vitro studies of the site of inhibitory action of omeprazole on adrenocortical steroidogenesis. Eur J Clin Pharmacol 1988;35: 625–9.

omeprazole

22P

4970

Title: Nasogastric Administration of Omeprazole for Control of Gastric PH

Matthew Carroll MD, Walter L. Trudeau MD
Division of GI, UC Davis

Acid peptic disease: epidemiology, pathogenesis, diagnosis, treatment >>>

INTRODUCTION: Numerous studies have established the efficacy of prophylactic therapy for the prevention of stress ulceration (SRMD). Maintenance of gastric pH > 4.0 is associated with a decreased incidence of UGI bleeding. Omeprazole is effective in reducing acid secretion, however, currently it is available in delayed-released capsule form only, an not indicated for intravenous or nasogastric administration. Recent reports describe the difficulties with nasogastric tube delivery of omeprazole via NG tube for stress ulceration prophylaxis. METHODS: 9 critically ill patients in the intensive care unit requiring stress ulceration prophylaxis were given omeprazole via NG tube at 20mg every 12 hours. Each capsule was opened, pellets crushed, mixed with 25cc of sodium bicarbonate solution (1meq/ml), and delivered via NG tube. Gastric pH was measured every 6 hours using nasogastric aspirate applied to Gastrocult slides. RESULTS: Patients maintained gastric pH above 5 over 99 % of the time. Gastric pH was maintained above 7 over 65 % of the time. There were no complications throughout the study period. CONCLUSION: Nasogastric administration of omeprazole is effective in controlling gastric pH in the ICU setting. The bioavailability appears to be preserved with the addition of a bicarbonate solution for delivery of the crushed pellets. Nasogastric administration of omeprazole for stress ulceration prophylaxis may prove to be less labor, intensive and more cost effective than IV cimetidine as well as having fewer side effects and drug interactions.

Omeprazole: Pharmacokinetics and Metabolism in Man

C. CEDERBERG, T. ANDERSSON & I. SKÅNBERG
Hässle Research Laboratories, Mölndal, Sweden

Cederberg C, Andersson T, Skånberg I, Omeprazole: pharmacokinetics and metabolism in man. Scand J Gastroenterol 1989, 24(suppl 166), 33–40

Omeprazole is acid labile and, therefore, has to be protected from exposure to the acidic gastric juice when given orally. Following a single oral dose of buffered suspension, omeprazole is rapidly absorbed with peak plasma concentrations within 0.5 hours. The volume of distribution is 0.3 litres/kg corresponding to the volume of extracellular water. In contrast to the long duration of antisecretory action, omeprazole is rapidly eliminated from plasma. The half-life is less than 1 hour, and omeprazole is almost entirely cleared from plasma within 3–4 hours. Omeprazole is completely metabolized in the liver. The two major plasma metabolites are the sulphone and hydroxyomeprazole, neither of which contributes to the antisecretory activity. About 80% of a given dose is excreted in the urine, and the remainder via the bile. The absorption of the coated granule formulation dispensed in hard gelatine capsules is slower, with peak concentrations 1–3 hours after dose. Bioavailability after a single dose is 35% and increases during repeated once-daily dosing to 60%. Omeprazole can potentially interact with the hepatic microsomal cytochrome P-450 enzymes. Studies show that the clearance of both diazepam and phenytoin are decreased and their terminal half-lives are increased during concomitant omeprazole treatment, both interactions being attributable to inhibition of hepatic metabolism. No interaction with propranolol or theophylline has been noted.

Key words: Drug interactions; omeprazole; pharmacokinetics

C. Cederberg, Gastrointestinal Clinical Pharmacology, AB Hässle, S-431 83 Mölndal, Sweden

Omeprazole reduces gastric acid secretion in both animals and man by inhibiting the gastric proton (acid) pump (H^+,K^+-ATPase) in the secretory membrane of the parietal cell. The compound is, however, acid labile and has to be protected from exposure to acidic gastric juice when given orally. The solubility in water is very low. In early experimental studies in man, omeprazole was, therefore, administered as an oral suspension in a sodium bicarbonate solution, together with additional bicarbonate solution given at the same time (1). Omeprazole has been given intravenously, dissolved in a 40% polyethylene glycol 400/water solution (2). This solution given with sodium bicarbonate to minimize acid degradation, has also been used for oral administration of ^{14}C-labelled omeprazole in many pharmacokinetic studies (3). These oral formulations were, however, unsuitable for clinical use, and omeprazole was subsequently formulated as enteric-coated granules (4). These granules were dispensed in ordinary hard gelatine capsules. This paper summarizes present knowledge of the pharmacokinetics and metabolism of omeprazole, with special reference to the relationship between plasma concentrations and effects on acid secretion.

PHARMACOKINETICS OF SINGLE DOSES

Omeprazole, given as a single oral dose in a buffered suspension or solution, is rapidly absorbed and peak plasma concentrations are achieved within 0.5 hours (1,5). After absorption, omeprazole is rapidly eliminated from the plasma with a terminal half-life of less than 1 hour. In most individuals, omeprazole is completely

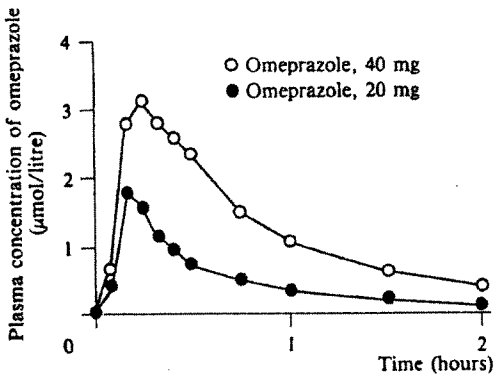


Fig. 1. Mean plasma omeprazole concentrations in 8 healthy subjects following a single oral dose of 20 or 40 mg as buffered suspension (data from Lind et al. (1)).

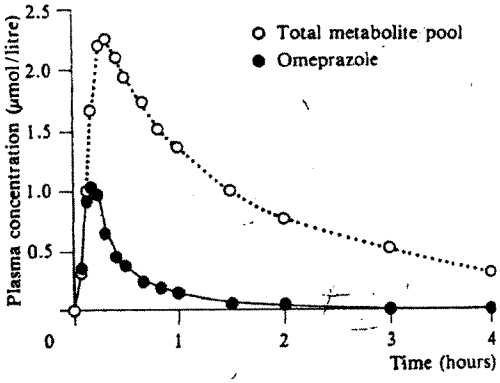


Fig. 2. Median plasma concentration-time curves for omeprazole and the total pool of radioactive metabolites in six healthy subjects following a single oral dose of ^{14}C-labelled omeprazole as a buffered solution (data from Regårdh et al. (3)).

cleared from the plasma within 3–4 hours (Fig. 1) (1). Studies with oral administration of ^{14}C-labelled omeprazole have shown that there is rapid and extensive formation of plasma metabolites (Fig. 2) (5). The plasma concentration-time curve for both omeprazole and the total pool of metabolites declined quickly indicating rapid elimination from the body; this is in contrast to the long duration of antisecretory action, which lasts for 3–4 days after a single dose (Fig. 3) (1, 3).

Thus, the degree of acid inhibition at any given time is independent of the plasma concentration of omeprazole or any of its metabolites. However, a significant correlation has been found between the degree of acid inhibition 2–4 hours after an oral dose and the area under the plasma

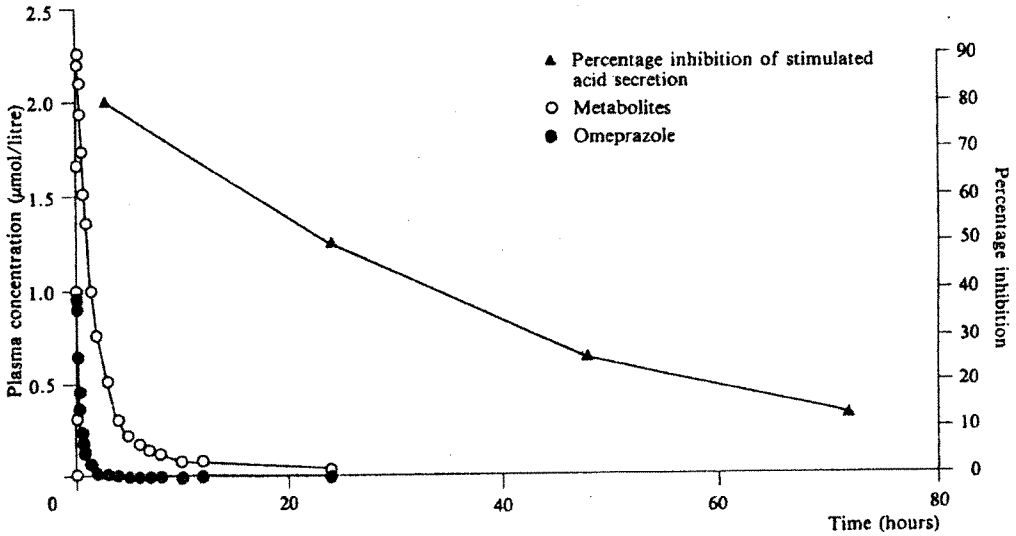


Fig. 3. Mean percentage inhibition of pentagastrin-induced acid secretion in six healthy subjects at various time points following a single oral dose of omeprazole, 20 mg, as buffered suspension (data from Lind *et al.* (1)) and median plasma concentration-time curves for omeprazole and the total pool of radioactive metabolites in six other healthy subjects following a single oral dose of ^{14}C-labelled omeprazole as a buffered solution (data from Regårdh et al. (3)).

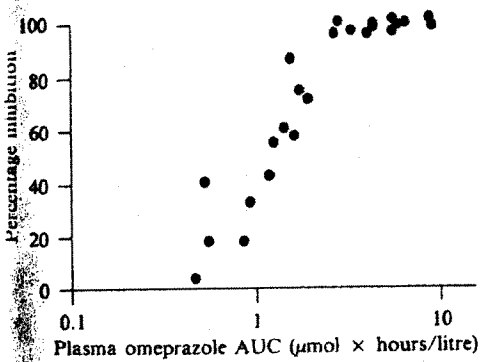


Fig. 4. Correlation between individual values for the area under the plasma omeprazole concentration-time curve (AUC) and percentage inhibition of pentagastrin-induced acid secretion 2–4 hours after various single oral doses of omeprazole buffered suspension in healthy subjects. Reproduced with permission from Lind et al. (1).

omeprazole concentration-time curve (AUC) (Fig. 4) (1). The omeprazole AUC reflects the product of the concentration of omeprazole in plasma and the time it is available in the systemic circulation and, therefore, available to the parietal cells.

Omeprazole is a lipophilic weak base. It is distributed into the parietal cells when available in the systemic circulation. Within the parietal cells omeprazole is concentrated in the acidic compartments because it is a weak base (6). In this acidic environment, omeprazole is protonated and chemically transformed to its active sulfenamide form, which binds and inactivates the proton transporting ATPase in the secretory membrane (6). The long-lasting binding of the active form of omeprazole to the H^+,K^+-ATPase in the parietal cells accounts for the lack of correlation between plasma concentration and degree of acid inhibition at any given time (6). Thus, the initial degree of acid reduction is dependent on the amount of drug available to the parietal cells, but the duration of acid inhibition is not dependent on sustained plasma concentrations.

METABOLISM AND ELIMINATION

After single oral and intravenous doses of ^{14}C-labelled omeprazole in young healthy subjects, about 80% of the radioactivity was detected in the urine and the remainder in the faeces (5). The amount recovered was similar for both routes of administration. No unchanged omeprazole was found in either the urine or the faeces. This suggests that omeprazole is completely metabolized before excretion. The bioavailability of the oral dose was about 50%, which indicates a fairly extensive first-pass metabolism.

The two main plasma metabolites in man have been identified as the sulphone and hydroxyomeprazole (Fig. 5) (5). The sulphone does not possess any antisecretory activity and hydroxyomeprazole is more than 100 times less potent than omeprazole (Wallmark B, personal communication). Some hydroxyomeprazole is excreted in the urine, but a fraction is probably further metabolized to the corresponding carboxylic acid, which has been identified in the urine (5). The sulphone, on the other hand, is only found in very small quantities in the urine and most seems to be further metabolized to more polar metabolites (5).

The biliary excretion of omeprazole has also been studied using intravenous administration of a very small (non-antisecretory) dose of radiolabelled omeprazole (7). During the first 4 hours, 16% of the given dose was recovered in the bile. As omeprazole is a weak base and, therefore, could be excreted via the acidic gastric juice, this route of excretion was also studied. However, negligible amounts (<1%) of the given dose were found in the gastric juice during the first 4 hours. It was concluded that the faecal recovery of omeprazole metabolites can be solely explained by biliary excretion and that this is the only important gastrointestinal route of elimination.

COMPARATIVE PHARMACOKINETICS

The pharmacokinetics of single oral and intravenous doses of radiolabelled omeprazole have been studied in different categories of patients (5,8). The mean plasma omeprazole concentration-time curves are shown in Fig. 6 and the pharmacokinetic variables summarized in Table I.

In patients with impaired renal function, the kinetics of unchanged omeprazole were essen-

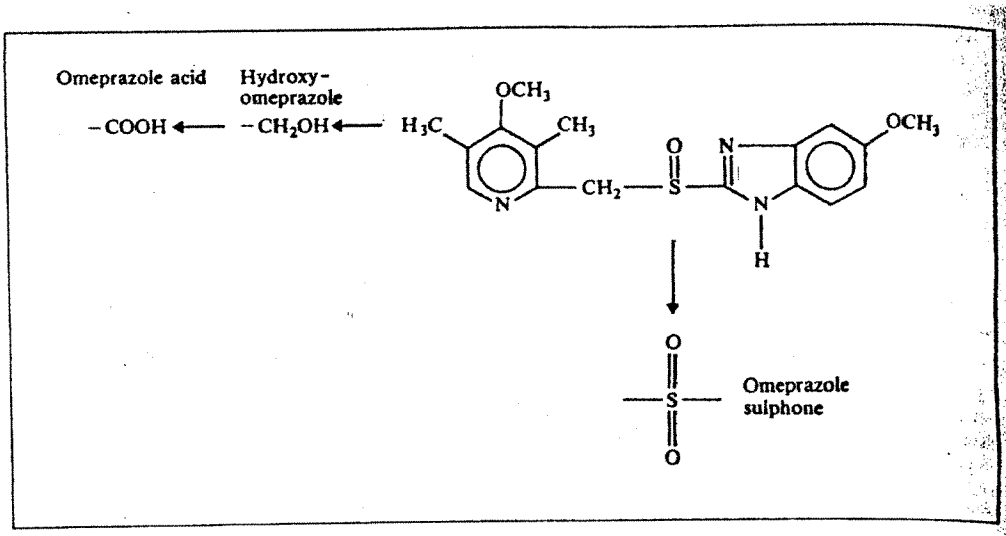


Fig. 5. Major metabolic pathways of omeprazole in man.

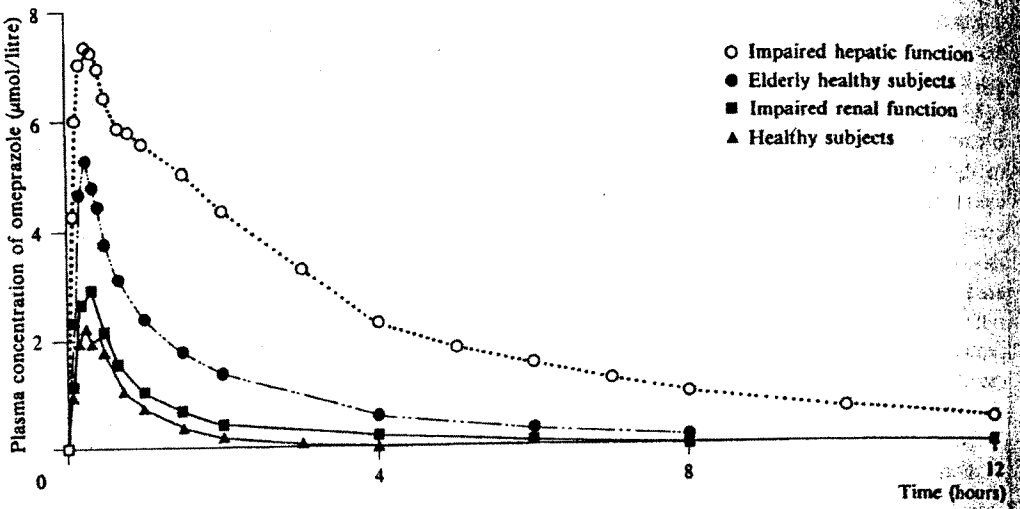


Fig. 6. Mean plasma concentration-time curves for omeprazole after a single oral dose of 40 mg, as a buffered solution in 18 young healthy subjects (3), 14 elderly healthy subjects (5), 12 patients with various degrees of renal function impairment (8), and 6 patients with various degrees of liver function impairment.

tially similar to those in healthy subjects. The rate of elimination of the total pool of metabolites was slower in these patients but, despite a marked reduction in kidney function, the elimination rate for the total pool of metabolites was such that no major accumulation is expected to occur during once-daily dosing (8). In elderly patients, the rate of elimination of omeprazole was on average slower and the bioavailability somewhat greater, while in patients with impaired hepatic function, the metabolism was considerably slower and the bioavailability close to 100%. It must be pointed

Table I. Pharmacokinetic variables for a single oral dose of omeprazole, 40 mg, in buffered solution and a single intravenous dose of omeprazole, 20 mg. Values are given as median with range. From the data referred to in Fig. 6

	Clearance (litres/minute)	Half-life (hours)	Vβ (litres/kg)	F
Young healthy subjects, n=18 (3)	0.62 (0.06–0.83)	0.50 (0.27–2.52)	0.32 (0.18–0.55)	0.46 (0.25–1.17)
Elderly healthy subjects, n=14 (5)	0.23 (0.08–0.48)	0.84 (0.49–2.00)	0.23 (0.22–0.34)	0.79 (0.33–1.14)
Patients with impaired hepatic function, n=8 (5)	0.07 (0.04–0.08)	2.68 (2.09–3.52)	0.20 (0.19–0.26)	0.98 (0.82–1.13)
Patients with impaired renal function, n=12 (8)	0.54 (0.27–0.93)	0.48 (0.34–0.93)	0.34 (0.27–0.48)	0.71 (0.10–1.24)

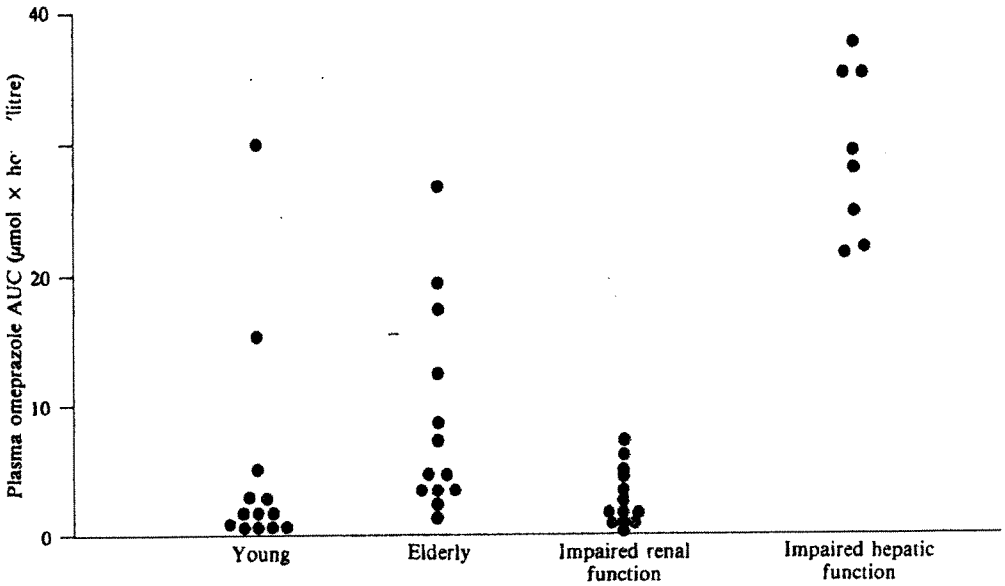


Fig. 7. Individual data for the area under the plasma omeprazole concentration-time curve (AUC) following a single oral dose of omeprazole, 40 mg, as a buffered solution. From the data referred to in Fig. 6.

out that the half-life of omeprazole in these patients was still as short as 2–4 hours. This suggests that the degree of general liver function impairment does not necessarily parallel the change in omeprazole metabolism, particularly as some young healthy subjects had similar half-l and plasma AUCs (Fig. 7).

The most important pharmacokinetic variable for the degree of antisecretory effect of omeprazole seems to be the plasma concentration AUC with which it has a close relationship. The range of individual data for the omeprazole AUC (Fig. 7) in most subjects was similar in healthy subjects and patients with impaired renal function. In elderly patients, the AUC was on average higher, but there was a considerable overlap with the last two categories. Patients with impaired hepatic function had a consistently higher AUC than normal subjects.

Two healthy subjects had much higher AUC values than others in their group. Their AUC values were in the same range as those found in

patients with impaired liver function. These variations in omeprazole metabolism in normal young subjects may possibly be due to genetic differences in drug metabolism, as has been described for other drugs (9). However, further studies are needed to clarify this.

DRUG INTERACTIONS

As omeprazole is extensively metabolized by the liver, presumably via the cytochrome P-450 system, interactions with other drugs also undergoing hepatic metabolism may occur.

In addition, omeprazole is a benzimidazole derivative and many imidazoles and benzimidazoles are known to inhibit hepatic microsomal oxidation (10). Therefore, several studies to determine possible interactions with other drugs have been performed (11–16). Concomitant omeprazole administration significantly inhibited the hepatic metabolism of phenytoin (11,13), diazepam (11), R-warfarin (15), aminopyrine (16) and antipyrine (16), but not of theophylline (15), S-warfarin (15) or propranolol (14). These changes were interpreted as an inhibition of the hepatic metabolism of these drugs.

The main results from these studies with omeprazole are summarized in Table II. The interaction with diazepam is unlikely to be of clinical significance. However, the elimination of phenytoin and warfarin is prolonged, and, in some patients, this may be clinically significant. Thus, monitoring of patients receiving these drugs concomitantly with omeprazole is recommended and a reduction in their dose may be necessary.

STUDIES WITH OMEPRAZOLE ENTERIC-COATED GRANULES

For clinical use, omeprazole is formulated as enteric-coated granules (4) which are dispensed in hard gelatine capsules. The absorption from this formulation was slower than that from a buffered solution or suspension. Peak plasma concentrations generally occurred 1–3 hours after the dose and the plasma concentration profile was, therefore, flatter and more extended in time (Fig. 8). The bioavailability was 35% after a single dose. Several studies have shown increased plasma omeprazole concentrations during once-daily dosing with the enteric-coated formulation in doses of 20–60 mg (17, 18). The bioavailability, as assessed by a simultaneous injection of a ^{14}C-labelled tracer dose of omeprazole, was increased to about 60% after 7 days' administration (data on file, AB Hässle).

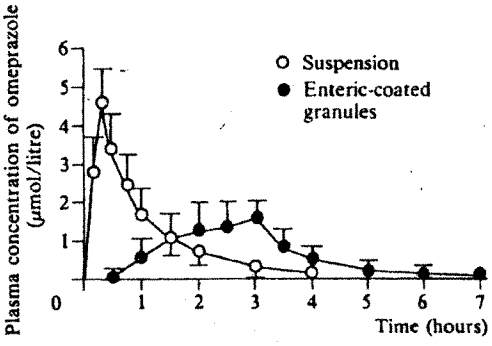


Fig. 8. Mean plasma concentration-time curves following a single oral dose of omeprazole, 60 mg, as buffered suspension or enteric-coated (EC) granules in six healthy subjects. Reproduced with permission from Pilbrant and Cederberg (4).

Table II. Effect of once-daily omeprazole, 20 mg, on the kinetics of concomitant drugs

Drug	Route	Dose	Effect	Source of data
Phenytoin	i.v.	250 mg*	Clearance decreased by 20%	Gugler & Jensen (11)
Diazepam	i.v.	0.1 mg/kg*	Clearance decreased by 27%	(Unpublished data)
Warfarin	p.o.	4.7 mg o.m.†	R-warfarin concentration increased by 12% S-warfarin concentration unchanged Coagulation time increased by 11%	Sutfin et al. (15)
Theophylline ‡	i.v.	2.5 mg*	No significant change	Gugler & Jensen (14)
Propranolol	p.o.	80 mg b.d.†	No significant change	Henry et al. (12)

*Single dose; †Repeated dosing; ‡Omeprazole, 40 mg.

The reason for this change is not fully understood, but may be due to decreased first-pass metabolism. However, increased absorption, due to the marked decrease in intragastric acidity obtained during treatment, may be contributory (18).

Several studies of both pentagastrin-induced gastric acid secretion (19,20) and 24-hour intragastric acidity (18, data on file, AB Hässle), during once-daily dosing with the enteric-coated formulation of omeprazole, have shown that the degree of acid inhibition increased during the first few days of administration. This increased pharmacological effect was, in most cases, associated with increased plasma concentrations. The increased acid inhibitory effect is, however, not only due to increased plasma concentrations, because a similar increase was seen in studies with repeated once-daily dosing with omeprazole, 10 mg intravenously, but in which plasma concentrations were unchanged (unpublished data). This latter increase can be explained by the long duration of the antisecretory action of omeprazole leading to an increase in the number of inhibited enzyme molecules during once-daily dosing. This effect does, however, seem to stabilize after 3–4 days (19), after which no further increase takes place (21).

The absorption from the enteric-coated formulation was not influenced by simultaneous food intake (22) or concomitant dosing with a high capacity antacid preparation (23).

REFERENCES

1. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole – a gastric proton pump inhibitor – on pentagastrin stimulated acid secretion in man. Gut 1983, 24, 270–276
2. Lind T, Moore M, Olbe L. Intravenous omeprazole: Effect on 24-hour intragastric pH in duodenal ulcer patients. Digestion 1986, 34, 78–86
3. Regårdh C-G, Gabrielsson M, Hoffmann K-J, Löfberg I, Skånberg I. Pharmacokinetics and metabolism of omeprazole in animals and man – an overview. Scand J Gastroenterol 1985, 20 (suppl 108), 79–94
4. Ibrant Å, Cederberg C. Development of an oral formulation of omeprazole. Scand J Gastroenterol 1985, 20 (suppl 108), 113–120
5. Regårdh C-G. Pharmacokinetics and metabolism of omeprazole in man. Scand J Gastroenterol 1986, 21(suppl 118), 99–104
6. Wallmark B, Brändström A, Larsson H. Evidence for acid-induced transformation of omeprazole into an active inhibitor of $(H^+ + K^+)$-ATPase within the parietal cell. Biochim Biophys Acta 1984, 778, 549–558
7. Lind T, Andersson T, Skånberg I, Olbe L. Biliary excretion of intravenous (^{14}C) omeprazole in humans. Clin Pharmacol Ther 1987, 42, 504–508
8. Naesdal J, Andersson T, Bodemar G et al. Pharmacokinetics of ^{14}C-omeprazole in patients with impaired renal function. Clin Pharmacol Ther 1986, 40, 344–351
9. Mayer UA. Molecular mechanisms of the dibrisoquine- and mephenytoin-polymorphisms: studies at the protein and DNA level and with circulating autoantibodies against P-450 buf 1 (db1) and P-450 meph. In: Miners J, Birkett DJ, Drew R, McManus M, eds. 7th international symposium on microsomes and drug oxidation. Taylor and Francis, Adelaide, London, 1988, 201–208
10. Dickins M, Bridges JW. The relationship between the binding of 2-n-alkylbenzimidazoles to rat hepatic microsomal cytochrome P-450 and the inhibition of monooxygenation. Biochem Pharmacol 1982, 31, 1315–1320
11. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. Gastroenterology 1985, 89, 1235–1241
12. Henry D, Brent P, Whyte I, Mihaly G, Devenish-Meares S. Propranolol steady-state pharmacokinetics are unaltered by omeprazole. Eur J Clin Pharmacol 1987, 33, 369–373
13. Prichard PJ, Walt RP, Kitchingman GK et al. Oral phenytoin pharmacokinetics during omeprazole therapy. Br J Clin Pharmacol 1987, 24, 543–545
14. Gugler R, Jensen JC. Drugs other than H_2-receptor antagonists as clinically important inhibitors of drug metabolism in vivo. Pharmacol Ther 1987, 33, 133–137
15. Sutfin T, Balmér K, Boström H, Eriksson S, Höglund P, Paulsen O. Stereoselective interaction of omeprazole with warfarin in healthy men. Ther Drug Monit (in press)
16. Henry DA, Somerville KW, Kitchingman G, Langman MJS. Omeprazole: effects on oxidative drug metabolism. Br J Clin Pharmacol 1984, 18, 195–200
17. Howden CW, Meredith PA, Forrest JAH, Reid JL. Oral pharmacokinetics of omeprazole. Eur J Clin Pharmacol 1984, 26, 641–643
18. Prichard PJ, Yeomans ND, Mihaly GW et al. Omeprazole: A study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 1985, 88, 64–69
19. Müller P, Seitz HK, Simon B, Dammann HG. Säuresekretionsverhalten und Plasmaspiegel unter einer mehrtägigen Omeprazole-Gabe. Arzneimittelforschung 1983, 33, 1685–1686
20. Howden CW, Forrest JAH, Reid JL. Effects of single and repeated doses of omeprazole on gastric acid and pepsin secretion in man. Gut 1984, 25, 707–710
21. Müller P, Seitz HK, Simon B et al. Vierwöchige

Omeprazole-Gabe: Einfluss auf Säureverhalten und basale Hormonspiegel. Z Gastroenterol 1984, 22, 236–240

22. Röhss K, Andrén K, Heggelund A, Lagerström PO, Lundborg P. Bioavailability of omeprazole given in conjunction with food. Acta Pharmacol Toxicol (Copenh) 1986, 59 (suppl 5), 85

23. Tuynman HARE, Festen HPM, Röhss K, Meuwissen SGM. Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules. Br J Clin Pharmacol 1987, 24, 833–835

Effect of Once Daily Intravenous and Oral Omeprazole on 24-Hour Intragastric Acidity in Healthy Subjects

C. CEDERBERG, K. RÖHSS, P. LUNDBORG & L. OLBE
Clinical Pharmacology, Astra Hässle AB, Mölndal, and Dept. of Surgery, Sahlgren's Hospital, Gothenburg, Sweden

Cederberg C, Röhss K, Lundborg P, Olbe L. Effect of once daily intravenous and oral omeprazole on 24-hour intragastric acidity in healthy subjects. Scand J Gastroenterol 1993;28:179–184.

The effect of repeated once daily administration of 20 mg omeprazole orally and 10 mg and 40 mg intravenously on 24-h intragastric acidity was studied in nine healthy subjects. On day 1, 20 mg orally and 10 mg intravenously reduced integrated intragastric acidity by 18% and 15%, respectively (NS). On day 5 the reduction had increased to 60% and 53%, respectively ($p < 0.05$). The first dose of 40 mg intravenously produced a reduction of 71% ($p < 0.05$) with no further increase during continued administration. An increase in plasma omeprazole concentrations by 56% ($p < 0.05$) was seen during repeated dosing with 40 mg intravenously, while no significant change occurred with the two other doses. Thus once daily administration of 10 mg omeprazole intravenously produced an effect on 24-h intragastric acidity comparable to that of once daily administration of 20 mg omeprazole orally. However, for both these dosage regimens it took a few days before their maximal effect was obtained. Parenteral administration of 40 mg omeprazole produced, already on the first day of treatment, an effect similar to that seen after 5 days of oral administration of 20 mg omeprazole or intravenous administration of 10 mg and can therefore overcome this initial delay in drug action. The reduction of 24-h intragastric acidity seen in the present study appeared to be lower than that seen in a similar study in duodenal ulcer patients, a finding not explained by differences in age or pharmacokinetics.

Key words: Healthy subjects; intragastric acidity; intravenous administration; omeprazole

C. Cederberg, Clinical Pharmacology, Astra Hässle AB, S-431 83 Mölndal, Sweden

Omeprazole is the first gastric proton pump inhibitor in clinical use and has been documented in the treatment of several acid-related disorders (1). In these studies omeprazole has been administered orally. For patients with acid-related disorders who are unable to take oral medication it is necessary to administer acid inhibitory drugs parenterally. Studies in healthy subjects have shown that omeprazole administered intravenously is about twice as potent as a corresponding oral dose for inhibition of pentagastrin-stimulated acid secretion (2), whereas earlier studies of 24-h intragastric acidity using intravenous omeprazole have suggested that this route of administration is less effective (3), a conclusion that was based on comparison between different studies. We therefore undertook this study to compare directly the effect of intravenous and oral omeprazole on 24-h intragastric acidity in the same individuals.

SUBJECTS AND METHODS

Subjects

Nine subjects, five men and four women, with a median age of 40 years (range, 35–48 years) and a median weight of 65 kg (range, 52–87) were included and completed the study. All subjects were regarded as healthy on the basis of a prestudy clinical examination including medical history, physical examination, ECG, and a routine laboratory screen. Informed written consent was obtained, and the study was conducted in accordance with the 'Declaration of Helsinki' as revised in Tokyo in 1975. Review and approval of the study was obtained from the Ethics Review Committee of the Faculty of Medicine at the University of Gothenburg and the Swedish Board of Health and Welfare.

Study drugs

Oral omeprazole was given as one hard gelatin capsule containing 20 mg omeprazole as enteric-coated granules. The capsule was taken in the morning before breakfast with a glass of water.

The intravenous formulation of omeprazole consisted of an ampoule with 40 mg of omeprazole as lyophilized sodium salt and 1.5 mg ethylenediaminetetraacetic acid (EDTA). Immediately before use the content of the ampoule was mixed with 100 ml of 0.9% NaCl (Travenol®). The final solution contained 4 mg omeprazole/ml. Omeprazole, 10 or 40 mg intravenously, was given over 30 min as 25 or 100 ml of this solution.

Study procedures

Within 14 days of inclusion each subject had a base-line 24-h intragastric acidity test. Each subject then took part in three study periods of 5 days each, separated by washout periods of at least 10 days. In each study period omeprazole,

10 mg intravenously, 40 mg intravenously, or 20 mg orally was given once daily in the morning. The order of treatments was randomized. On day 1 in each study period the subject came to the Clinical Pharmacology Laboratory (CPL) in the morning, having fasted from 2200 h the previous day. A nasogastric tube (10 FG) was passed and positioned in the most distal part of the stomach. The position was checked by a water recovery test. At 0800 h a sample (5 ml) of gastric juice was aspirated, after which omeprazole was given in accordance with the subject's randomization. From 0900 h until 0800 h the next morning hourly samples of gastric juice were aspirated. In each sample, pH was recorded to the nearest 0.01 unit by means of a combined glass and reference electrode and a pH meter (Radiometer, Copenhagen). The electrode was calibrated with standard buffers of pH 2.01, 4.03, and 7.00 both before and after the study. During the study day serial blood samples were taken in heparinized tubes from an indwelling cannula in a forearm vein, and plasma omeprazole concentrations determined by high-performance liquid chromatography (HPLC) (4).

Standardized meals were served at 0830, 1230, and 1830 h. Food, liquid, and cigarette consumption was carefully recorded during the base-line intragastric acidity test, and this schedule was adhered to during all subsequent 24-h tests.

On days 2–4 the oral medication was taken by the subject at home as instructed. The intravenous medication was given each morning at 0800 h at the CPL. On day 5 the intragastric acidity test was repeated, during which the 5th dose of omeprazole was given. Blood samples for omeprazole determinations were taken as on day 1.

Within 4 days after the end of the 3rd study period each subject had the preinclusion laboratory screen repeated.

Calculations and statistics

Intragastric acidity was expressed both as pH and as mmol/l equivalents, which is the concentration of hydrogen ions that in an ideal solution would have a corresponding activity. Mmol/l equivalents were calculated as $10^{-pH} * 1000$. The integrated 24-h intragastric acidity was calculated from each experiment as the area under the mmol/l-equivalent time curve by means of the trapezoidal formula and expressed as mmol*h/l. The area under the plasma omeprazole concentration time curve (AUC) was also calculated by means of the trapezoidal formula. For the intravenous doses the AUC was extrapolated to infinity by adding the residual area calculated as the last measured plasma concentration divided by the elimination rate constant (β). This rate constant was determined by log-linear regression of the terminal slope of the plasma concentration time curve. Pharmacokinetic variables for the intravenous experiments were calculated as follows: $t_{1/2} = 0.693/\beta$; systemic clearance (CL) = dose/AUC. The bioavailability (F) of the oral 20-mg dose was calculated by using the AUC for the corresponding 10-mg intravenous dose multiplied by 2 and expressed as percentage. Statistical comparisons were made

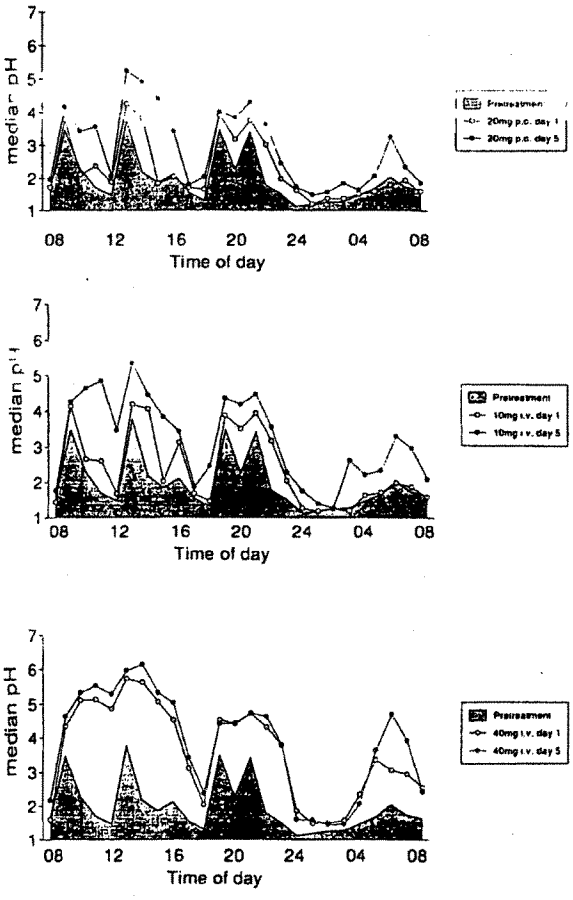


Fig. 1. Median intragastric pH profile in nine healthy subjects before treatment and on days 1 and 5 of once daily administration of omeprazole in doses of 20 mg orally and 10 mg and 40 mg intravenously.

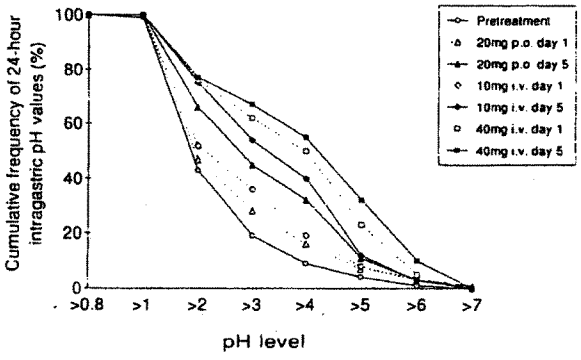


Fig. 2. Mean cumulative intragastric pH frequency profiles in nine healthy subjects before treatment and on days 1 and 5 of once daily administration of omeprazole in doses of 20 mg orally and 10 mg and 40 mg intravenously.

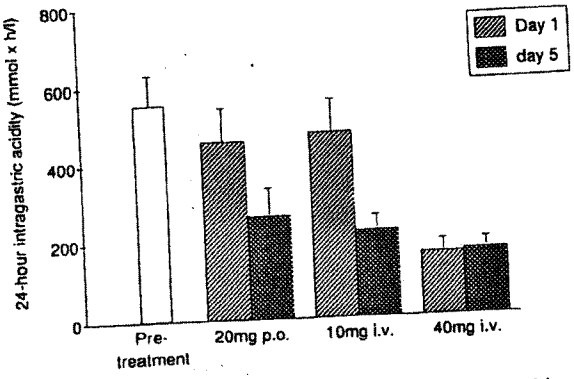


Fig. 3. Integrated 24-h intragastric acidity in nine healthy subjects before treatment and on days 1 and 5 of once daily administration of omeprazole in doses of 20 mg orally and 10 mg and 40 mg intravenously. Values are given as mean with SEM.

by means of the Wilcoxon matched-pairs signed-rank test with a p value of less than or equal to 0.05 regarded as significant.

RESULTS

Intragastric acidity

The median 24-h intragastric acidity profiles are shown as pH in Fig. 1, and the mean cumulative intragastric pH frequency profiles in Fig. 2. Compared with pretreatment the first oral dose of 20 mg omeprazole reduced the mean 24-h integrated intragastric acidity by 18% (Fig. 3). This difference was, however, not statistically significant ($p = 0.173$). After an additional 4 days' treatment the reduction had increased to 53% ($p = 0.008$). The first intravenous dose of 10 mg omeprazole also failed to produce a statistically significant reduction (15%) when compared with pretreatment ($p = 0.374$). After an additional 4 days of dosing integrated 24-h intragastric acidity had decreased significantly ($p = 0.008$) and was 60% compared with pretreatment (Fig. 3). The extent of reduction of 24-h intragastric acidity was similar for the 10-mg intravenous and 20-mg oral dosage regimens both on day 1 ($p = 0.374$) and on day 5 ($p = 0.813$) (Fig. 3).

The first intravenous dose of 40 mg omeprazole produced a pronounced and statistically significant ($p = 0.008$) reduction in integrated intragastric acidity of 71% (Fig. 3). After 4 additional days of administration the reduction in integrated intragastric acidity was similar to that on day 1, being 70% (Fig. 3). The effect of the first dose of 40 mg intravenously on 24-h intragastric acidity was not significantly different from that seen after 5 days of 20 mg orally ($p = 0.441$) (Fig. 3).

Pharmacokinetics

The mean plasma omeprazole concentration time curves are shown in Fig. 4, and the pharmacokinetic variables are summarized in Table I. Plasma concentrations after once daily oral administration of 20 mg omeprazole increased in seven of the nine subjects from day 1 to day 5, but the difference was not statistically significant ($p = 0.11$). The geometric mean change was 35% (−16% to 118%). During 5 days of once daily administration with intravenous omeprazole a significant increase in plasma concentrations was seen with the 40-mg dose ($p = 0.011$) but not with the 10-mg dose ($p = 0.441$). The geometric mean change was 56% (22–99%) and 6% (−6% to 19%) for the 40- and 10-mg doses, respectively. Omeprazole clearance was similar for 10 and 40 mg intravenously on day 1, with a geometric mean ratio (10 mg/40 mg) of 0.90 (0.74–1.05), indicating linear kinetics in this dose range. After 5 days of once daily dosing, clearance had decreased significantly ($p = 0.011$) by 36% (18–50%) for the 40-mg dose, whereas no such change was seen with 10 mg (−6%; −16% to 6%). Thus the kinetics became non-linear on day 5 in this dose range (Table I). The terminal plasma half-life was not changed during 5 days of intravenous administration with either 10 mg ($p = 0.374$) or 40 mg ($p = 0.139$) (Table I).

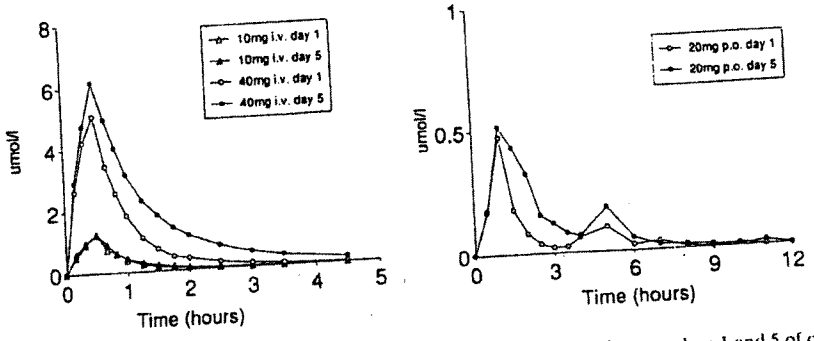


Fig. 4. Mean plasma omeprazole concentration profiles in nine healthy subjects on days 1 and 5 of once daily administration of omeprazole in doses of 20 mg orally and 10 and 40 mg intravenously.

Table 1. Summary of pharmacokinetic data in nine healthy subjects during once daily administration of omeprazole. Values are given as geometric mean with 95% confidence interval

	10 mg intravenously		40 mg intravenously		20 mg orally	
	Dose 1	Dose 5	Dose 1	Dose 5	Dose 1	Dose 5
AUC	0.93	0.99	4.25	6.59	0.62	0.84
(μmol*h/l)	0.70–1.25	0.74–1.32	3.45–5.22	4.33–10.0	0.39–0.99	0.41–1.74
Clearance	516	488	454	292	—	—
(ml/min)	386–692	369–653	369–558	192–445		
$t_{1/2}$(h)	0.51	0.58	0.69	0.75	—	—
	0.41–0.66	0.49–0.69	0.58–0.81	0.60–0.97	—	—
F(%)	—	—	—	—	33	Not
					23–46	calculated*

* Because of possible non-linear kinetics on day 5.

Tolerability

Omeprazole was well tolerated, and no clinically significant changes in laboratory variables were found. Adverse experiences were mild to moderate, and none was considered serious, clinically important, or related to drug exposure.

DISCUSSION

Assessment of the antisecretory effect of an acid inhibitor can be made in several ways. The formal approach is to measure quantitatively the output of acid either spontaneously or during stimulation of acid secretion. This includes measurements of both total volume output and the acid concentration by titration to pH 7. During the last 10–15 years an increased interest in the effects of antisecretory compounds on intragastric acidity has occurred, especially since the introduction of intragastric pH probes (5). These measurements determine the activity of hydrogen ions in gastric juice (6) and have been proposed to be more closely related to the clinical effects that these compounds have in the treatment of peptic ulcer disease (7). There are currently two ways of measuring intragastric acidity. One is to aspirate small samples repeatedly through a nasogastric tube; the other is to use an intragastric pH probe. We have in this study used the aspiration technique because of previous experience with this method and data suggesting that the two methods are compatible (8). There are at present many suggestions how to analyse data from 24-h intragastric acidity measurements (9). They can either be analyzed by using the original pH values or be converted to mmol/l equivalents. The latter takes full account of the great difference in hydrogen ion activity between pH 1 and 2 and less account of the small changes that occur above pH 3, whereas an analysis of pH values takes similar account of changes irrespective of magnitude of change in hydrogen ion activity. At present there is no uniform agreement on how to best present such data. We have therefore presented our data both as pH and as mmol/l equivalents. We have also included a cumulative pH profile instead of presenting the data as time above a specific pH value. This will allow any reader to reanalyze the data at any given pH value.

The results of the present study show that during treatment with lower doses of omeprazole (10 mg intravenously and 20 mg orally) once daily there is an increase in antisecretory effect during the first 5 days of treatment irrespective of route of administration. However, during once daily dosing with 40 mg intravenously there was no such increase in antisecretory effect despite a significant increase in plasma omeprazole concentrations. During repeated administration of 10 mg intravenously there was no significant change in plasma concentrations, whereas there was a trend towards an increase during treatment with 20 mg orally. Thus, the increase in pharmacologic effect seen during the first 5 days of once daily dosing must also be due to factors other than increased plasma concentrations. We have previously suggested that this increased antisecretory effect during repeated once daily administration is due to an increase in the number of H^+,K^+-ATPase enzyme molecules inhibited. The fact that there was no further increase in antisecretory effect during repeated administration of 40 mg intravenously, despite increased plasma concentrations, suggests that this dose causes a maximal effect already after the first dose. Previous studies in dogs have shown that the duration of action cannot be prolonged by supramaximal doses (10). This suggests that the 40-mg intravenous dose initially produces a maximal effect but that the duration of action in this group of subjects is not sufficient to cause a complete reduction of intragastric acidity during a 24-h period. This implies that multiple daily doses of omeprazole are probably needed to increase the effect on 24-h intragastric acidity further in healthy subjects.

On day 1, 10 mg intravenously and 20 mg orally produced a similar reduction in integrated 24-h intragastric acidity (15% versus 18%), but plasma omeprazole AUC was somewhat higher (0.90 versus 0.63) for 10 mg intravenously. This could be interpreted to indicate that the intravenous route of administration is less effective in relation to the plasma omeprazole AUC achieved. On day 5, however, 10 mg intra-

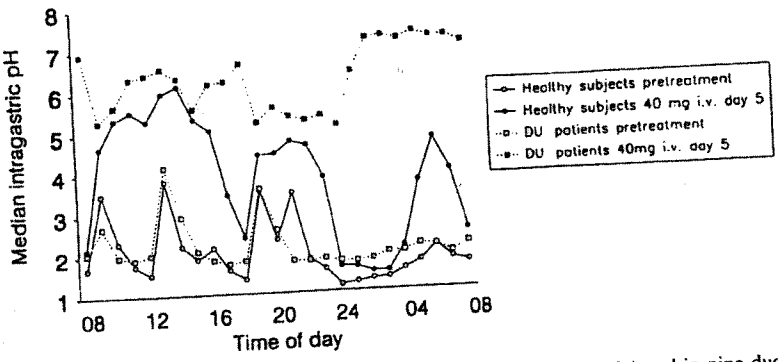


Fig. 5. Median intragastric pH profiles in nine healthy subjects (present study) and in nine duodenal ulcer (DU) patients (from Ref. 13) before treatment and on day 5 of once daily administration of 40 mg omeprazole intravenously.

venously was slightly more effective (60% versus 53%), a finding consistent with the slightly higher plasma omeprazole AUC (0.99 versus 0.83). The intravenous route of administration is, however, twice as effective when assessed on a milligram per milligram base. We have currently no explanation of the slight discrepancy in the correlation between plasma omeprazole AUC and reduction of integrated 24-h intragastric acidity between 10 mg intravenously and 20 mg orally on day 1. Comparative studies between intravenous and oral administration using both pentagastrin-stimulated gastric acid secretion (2) and 24-h intragastric acidity (11) have not indicated such discrepancies.

Increasing plasma concentrations of omeprazole during the first days of administration with both intravenous and oral omeprazole have previously been reported by us and others (11–13). The reason for this is most likely an inhibition of cytochrome P450 IIC18 by omeprazole, thus inhibiting one of its major metabolic pathways (14, 15). The results from the present study are in agreement with those from a previous comparative study of intravenous and oral omeprazole in duodenal ulcer (DU) patients (11), with the exception that the degree of antisecretory effect appears to be higher in DU patients. This difference was most apparent for the 40-mg intravenous dose (Fig. 5). The greatest difference was seen during the last 12 h of the dose interval, when there was a marked decrease in intragastric pH in healthy subjects, whereas no such decrease in pH was seen in DU patients. This difference cannot be explained by differences in pharmacokinetics or age, since the plasma omeprazole AUC and $t_{1/2}$ were similar in the two groups, and they were of comparable age. Since the major difference was in the latter part of the dose interval, one might speculate that there is a difference in the rate of recovery of acid secretion between healthy subjects and DU patients. Such a difference could be due to differences in the rate of de novo synthesis of ATPase molecules, resulting in a longer duration of action of omeprazole in DU patients. There are, however, no data to support such a speculation. The mean plasma omeprazole AUC after 20-mg oral administration on day 5 in the present study (0.84 μmol*h/l) was numerically lower than that seen in DU patients (1.88 μmol*h/1) (11), a finding consistent with the more marked reduction in intragastric acidity seen in these patients.

Many pharmacologic studies are done in healthy subjects, and results are often extrapolated to patients. The apparent difference in the degree of pharmacologic effect seen in these two studies with omeprazole suggests that such extrapolations should be done with caution. The relative differences between doses were, however, similar in the two studies.

REFERENCES

1. Walan A. Clinical experience with omeprazole: assessment of efficacy and safety. Gastroenterol Hepatol 1989;4 Suppl 2:27–33.
2. Jansen JBMJ, Lundborg P, Baak LC, et al. Effects of single and repeated intravenous doses of omeprazole on pentagastrin stimulated gastric acid secretion and pharmacokinetics in man. Gut 1988;29:75–80.
3. Walt RP, Reynolds JR, Langman MJS, et al. Intravenous omeprazole rapidly raises intragastric pH. Gut 1985;26:902–6.
4. Lagerström P-O, Persson B-A. Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. J Chromatogr 1984;308:347–56.
5. Walt R. Twenty-four hour intragastric acidity analysis for the future. Gut 1986;27:1–9.
6. Emde C. Electrochemical aspects of pH electrodes. Dig Dis 1990;8 Suppl 1:18–22.
7. Burget D, Chiverton S, Hunt R. Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression. Gastroenterology 1990;99:345–51.
8. Dammann H, Dreyer M, Kangah R, Wolf N. Gastric aspiration technique for pH recordings: a critical evaluation of this method. Dig Dis 1990;8 Suppl 1:3–9.
9. Röhmel J, Merki H, Wilder-Smith C, Walt R. Analysis and statistical evaluation of continuous pH recordings. Dig Dis 1990;8 Suppl 1:87–96.
10. Carlsson E, Larsson H, Mattsson H, Ryberg B, Sundell G. Pharmacology and toxicology of omeprazole—with special ref-

erence to the effects on the gastric mucosa. Scand J Gastroenterology 1986;21 Suppl 118:31–8.
11. Cederberg C, Thomson A, Mahachai V, et al. Effect of intravenous and oral omeprazole on 24-hour intragastric acidity in duodenal ulcer patients. Gastroenterology 1992;103:913–8.
12. Andersson T, Cederberg C, Heggelund A, Lundborg P. The pharmacokinetics of single and repeated once daily doses of 10, 20, and 40 mg omeprazole as enteric coated granules. Drug Invest 1991;3:45–52.
13. Prichard P, Yeomans N, Mihaly G, et al. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 1985;88:64–99.
14. Andersson T, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clin Pharmacol Ther 1990;47:79–85.
15. Romkes M, Faletto M, Blaisdell J, Raucy J, Goldstein J. Cloning and expression of complementary DNAs for multiple members of the human cytochrome P450IIC subfamily. Biochemistry 1991;30:3247–55.

Received 21 April 1992
Accepted 31 August 1992

Drugs 47 (2): 305-317, 1994
0012-6667/94/0002-0305/$06.50/0

Antacids
Indications and Limitations

Chi-Kong Ching and *Shiu-Kum Lam*

Division of Gastroenterology and Hepatology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

Contents

305 Summary
307 1. Peptic Ulcer Disease
307 1.1 How Efficient are Antacids in Ulcer Healing?
308 1.2 What is the Best Way to Administer Antacids
308 1.3 Does Cigarette Smoking Affect Antacid Healing?
309 1.4 Does Antacid Healing Lead to Longer Remission?
309 1.5 Does the Combination of an Antacid Plus an Anticholinergic Offer Any Advantage?
309 1.6 Do Antacids Prevent Ulcer Recurrence?
309 2. How Do Antacids Work in Peptic Ulcer Disease?
309 2.1 Reduction of Postprandial Acid Secretion
310 2.2 Cytoprotection
310 2.3 Bile Acid Binding
310 3. Gastro-Oesophageal Reflux Disease
311 3.1 Medical Therapy for GORD
311 3.2 Relief of Reflux Symptoms by Antacids
311 3.3 Healing of Reflux Oesophagitis by Antacids
311 3.4 Recommendations
312 4. Stress Ulcer Syndrome
312 4.1 Prophylactic Treatment for Acute Stress Ulcer Syndrome
312 5. Pregnancy- and Delivery-Associated Reflux and Complications
313 6. Miscellaneous Use of Antacids
313 6.1 Nonulcer Dyspepsia
314 6.2 Nonsteroidal Anti-Inflammatory Drug-Induced Upper Gastrointestinal Mucosal Damage
314 7. Conclusions

Summary Antacids have served us well for over a century. In terms of peptic ulcer disease, the attitude in the late 1950s to 1970s that antacids should be taken only on demand was unjustified and erroneous. 13 recent endoscopic controlled studies have confirmed the efficacy of antacids in the healing of duodenal ulcer, achieving about 75% healing in 4 weeks. The efficacy of antacids in promoting gastric ulcer healing has been less well studied and the results are controversial. The most appropriate and economical antacid regimens for the treatment of duodenal ulcer disease should include tablets or liquid that have acid neutralising capacity of 400 mmol/day given at least an hour after meals. As a long term therapy, antacids appear to work, but need be taken in multiple daily doses, a regimen which is unlikely to meet with long term patient compliance.

Patients with gastro-oesophageal reflux disorders or pregnancy-related reflux have also benefited from the usage of antacids *ad libitum*. Early previous studies have clearly demonstrated the efficacy of antacids in reducing gastro-oesophageal reflux and healing of reflux oesophagitis. The acidity of the gastric contents is the major determining factor in the outcome of the aspiration pneumonitis occurring during delivery. The prophylactic use of antacids during delivery has helped to reduce the severity of this complication. Similarly, the prophylactic administration of antacid aiming to maintain gastric pH between 3.5 to 7.0 has resulted in significant reduction of bleeding due to stress associated ulcers and/or erosive haemorrhagic gastritis in critically ill patients. Antacid therapy, however, is controversial in the management of nonulcer dyspepsia or nonsteroidal anti-inflammatory drug related upper gastrointestinal mucosal damage.

Undoubtedly, antacids have major roles to play in the treatment of gastric acid related disorders. They have clear advantages and disadvantages when compared with the antisecretory agents. New proton pump inhibitors in particular have certainly superseded antacids and even the H_2-receptor antagonists in many respects. However, the long term safety record of antacids remains unsurpassed by any of the new antisecretory agents.

The use of antacids probably began in the first century when Celsus used neutralising earths for the treatment of abdominal distress (Crohn & Rosenak 1935). Their formal use as an ulcer healing agent probably started in 1856, when William Brinton employed bicarbonate of potash in combination with bismuth to treat patients with gastric ulcer disease (Brinton 1865). Bertram Sippy in 1915 (Sippy 1915), following the pronouncement by Schwarz in 1910 of his famous dictum, 'no acid - no ulcer' (Schwarz 1910), pioneered the scientific use of antacids to treat peptic ulcer disease.

In the following 50 years, antacids were widely used and their popularity grew further. In 1952, Pickering demonstrated that neutralisation of the acid gastric contents helped to relieve pain induced by peptic ulcer (Pickering 1952). However, antacid therapy lost its momentum over the next 2 decades. Although they were still generally prescribed for peptic ulcer, antacids were usually given with the advice that a small quantity need only be taken when pain occurred. This was based on the concept, now known to be erroneous (Lam 1988), that dangerously large doses of antacid were necessary to neutralise gastric acidity and that antacids were unable to heal peptic ulcers.

The downfall of enthusiasm for antacid therapy coincided with the introduction of carbenoxalone ('Biogastrone') and later cimetidine. These new agents quickly caught the attention of most investigators who were then armed with 2 powerful tools: the endoscope as an end-point detector of ulcer healing and the method of randomised, controlled trial as a decision maker.

Using these 2 tools, Peterson et al. (1977) and Lam et al. (1979) attempted, with little success, to bring the attention of ulcer therapists back to antacids. Both of these studies showed that antacids healed about 75% of duodenal ulcers at the end of 4 weeks and that antacids were significantly superior in efficacy to placebo. They, however, used 7 doses of antacids daily in both protocols. The method, therefore, posed the problem of patient compliance. Despite a 5-fold difference in the quantity of antacid used, there was very little difference in the rates of healing duodenal ulcers between these 2 studies. Thus, there is very little doubt that antacids, even at low doses, accelerate ulcer healing.

Antacid therapy has similarly enjoyed a period of success in the treatment of gastro-oesophageal reflux disease (GORD), acute stress ulcer prophylaxis, and pregnancy-associated reflux disease as well as prophylaxis during delivery. These observations therefore raise a number of fundamental questions regarding the therapeutic mechanisms of the antacid. We aim to review the past, present and future roles of antacids in the management of upper gastrointestinal disorders. We consider the literature cited here to be important and relevant, but by no means exhaustive.

Table I. Efficacy of antacids in duodenal ulcer healing at 4 weeks in various comparative trials. Antacid dosages are given in the form of their acid-neutralising capacity

Study	Agents	Antacid			Placebo			H_2-antagonists		
		n	no. healed	%	n	no. healed	%	n	no. healed	%
Comparisons with placebo										
Berstad et al. (1982)	Antacid 280 mmol/day	37	30	81	38	9	24			
Faizallah et al. (1984)	Antacid 1080 mmol/day	37	18	49	32	8	25			
Kumar et al. (1984)	Antacid 103 mmol/day	77	56	72	24	7	29			
Lam et al. (1979)	Antacid 175 mmol/day	26	20	77	24	8	33			
Peterson et al. (1977)	Antacid 1008 mmol/day	36	28	78	38	17	45			
Weberg et al. (1985)	Antacid 120 mmol/day	38	28	74	38	11	29			
Comparisons with H_2-receptor antagonists										
Becker et al. (1987)	Antacid 595 mmol/day *vs* cimetidine 800 mg/day	34	28	83				33	23	69
Bianchi Porro et al. (1986a)	Antacid (unknown dosage) *vs* cimetidine 800 mg/day	39	28	72				39	26	67
Fedeli et al. (1979)	Antacid 560 mmol/day *vs* cimetidine 1000 mg/day	24	18	75				27	21	78
Ippoliti et al. (1978)	Antacid 861 mmol/day *vs* cimetidine 1200 mg/day	32	19	59				33	21	64
Lauritsen et al. (1985a)	Antacid 600 mol/day *vs* ranitidine 300 mg/day	25	21	84				28	25	89
Lux et al. (1986)	Antacid 280 mmol/day *vs* cimetidine 1000 mg/day	86	69	80				85	63	75
Weberg et al. (1988)	Antacid 120 mmol/day *vs* cimetidine 800 mg/day	76	54	71				74	58	78
Total		567	468	69	194	60	30	319	237	74

I. Peptic Ulcer Disease

1.1 How Efficient Are Antacids in Ulcer Healing?

The general efficacy of antacids in comparative trials versus placebo and histamine H_2-receptor antagonists are presented in table I.

1.1.1 Duodenal Ulcer

There are now a total of 6 placebo-controlled studies of antacid in this therapeutic area (Berstad et al. 1982; Faizallah et al. 1984, Kumar et al. 1984; Lam et al. 1979; Peterson et al. 1977; Weberg et al. 1985). These all show that antacids work significantly better than placebo in healing duodenal ulcer, achieving about 75% healing at the end of 4 weeks (table I). Seven other studies (Becker et al. 1987; Bianchi Porro et al. 1986a; Fedeli et al. 1979; Ippoliti et al. 1978; Lauritsen et al. 1985a; Lux et al. 1986; Weberg et al. 1988) compared the efficacy of antacids with that of H_2-receptor antagonists and were unable to find a significant difference (table I). These leave little doubt that antacids are effective for duodenal ulcer healing.

1.1.2 Gastric Ulcer

The evidence in support of the efficacy of antacid in the treatment of gastric ulcer is much less convincing than that in relation to duodenal ulcer. Of the 4 studies employing endoscopic assessment, 2 demonstrated that antacids were signifi-

cantly better than placebo (Hollander & Harlan 1973; Rydning et al. 1986). The other 2 studies showed that the healing rates were similar in the antacid, cimetidine and placebo groups (Isenberg et al. 1983; Pace et al. 1985).

1.2 What is the Best Way to Administer Antacids?

Antacids should be given 1 and 3 hours after each of the 3 main meals of the day as well as at bedtime. Evidence is accumulating, however, that antacids can be prescribed in a much more convenient way than has been conventionally established.

1.2.1 Liquid or Tablet Forms?

Liquid dosage forms have always been considered more effective, but less convenient, than tablets. Previous *in vitro* experiments showed that acid neutralisation can be more quickly and effectively achieved with liquid antacids (Lam 1988). However, better tablet formulations have become available in recent years. A recent *in vivo* study indicates that intragastric pH measurements are identical after administration of the liquid form and the tablet form of one antacid preparation (Berstad & Weberg 1986). It may, thus, be irrelevant except in terms of cost-effectiveness (Drake & Hollander 1981) to choose between liquid and tablet forms for symptomatic relief.

It seems wiser to recommend antacids with high neutralising capacity that are inexpensive. Furthermore, clinical trials have clearly demonstrated the efficacy of antacid tablets in ulcer healing (Berstad et al. 1982; Lam 1988; Weberg et al. 1985). Because of their convenience, effective acid-neutralising capacity and clinical efficacy, tablet forms are likely to be more popular.

1.2.2 Seven Times a Day or Four Times a Day?

Most reported studies are based on a dosage scheme of at least 6 times a day, i.e. 1 and 3 hours after each of the 3 main meals of the day. Success, however, has been reported with 5 doses a day (Bianchi Porro et al. 1986b), 4 doses a day (1 hour after meals and at bedtime) [Lux et al. 1986; Weberg et al. 1985], or simply as needed for pain (Faizallah et al. 1984). It seems likely that the originally proposed cumbersome regimen of 7 times a day is unnecessary, and a more convenient regimen can be adopted.

1.2.3 High Dose or Low Dose?

The individual doses of antacids reported varied immensely, with neutralising capacities ranging between 100 and 1000 mmol. Duodenal ulcer healing rates after 4 weeks of treatment in different ethnic groups varied with the use of antacid doses having different daily neutralising capacities (Lam 1991). It is apparent that despite known differences in acid secretory capacity in different races (being low, for example, in individuals from China or India when compared with Caucasians, there is a steep rise in healing rates with even a small increase in antacid dose, reaching a plateau at about 200 mmol. Thus a dose with a daily neutralising capacity of around 400 mmol (to allow for safety margins and better symptomatic relief) may prove to be applicable to all ethnic groups, and this would make the occurrence of adverse effects minimal. Unlike that seen with other ulcer healing agents, the difference in cost after doubling the daily antacid consumption is insignificant. This is certainly affordable even in the third world or developing countries.

1.3 Does Cigarette Smoking Affect Antacid Healing?

Cigarette smoking consistently delays duodenal ulcer healing by placebo in the majority of previous studies and the effect is highly significant when the results are pooled together (Lam 1991). An adverse effect of cigarette smoking on duodenal ulcer healing has also been observed in patients treated with antacids, and the effect is also highly significant after meta-analysis (Lam et al. 1987). In this respect, antacids behave like other acid-reducing agents such as H_2-receptor antagonists and omeprazole, with which the adverse smoking effect is less consistently seen than with placebo,

but becomes
ious studies
Only 1 st
rette smokin
and no harm
al. 1986).
smoking did
of gastric ul
nists (McInt
on post-treat
tenance trea

1.4 Does to Longe

The rela
carbenoxol
have been l
H_2-receptor
Cook et al.
1981). This
bacter pylo
spect? Sinc
protective
behave sin
compounds
acid-reduci
Three st
relapse rate
or H_2-rece
Bresci et al
rates were
group and
group). Th
healing wit
tor antago
(Bardhan e
al. 1985b; I

1.5 Does an Antic

Before
acid/antich
er's favour
bination w
(Strom et a

but becomes highly significant when results of various studies are pooled (Lam 1991).

Only 1 study has examined the effect of cigarette smoking on gastric ulcer healing by antacids and no harmful effects were observed (Rydning et al. 1986). Generally speaking, it appears that smoking did not exert any ill effect on the healing of gastric ulcer by antacids or H_2-receptor antagonists (McIntosh et al. 1985). The effect of smoking on post-treatment relapse and relapse during maintenance treatment with antacids is not known.

1.4 Does Antacid Healing Lead to Longer Remission?

The relapse rates following initial healing by carbenoxolon, colloidal bismuth and sucralfate have been lower than those following healing by H_2-receptor antagonists (Coghlan et al. 1987; Cook et al. 1980; Lam et al. 1987; Martin et al. 1981). This is unrelated to eradication of *Helicobacter pylori*. How do antacids behave in this respect? Since aluminium antacids may be cytoprotective (Tarnawski et al. 1990), do antacids behave similarly to these other cytoprotective compounds? Or do antacids act more like other acid-reducing agents?

Three studies have compared the duodenal ulcer relapse rates following initial healing with antacids or H_2-receptor antagonists (Becker et al. 1987; Bresci et al. 1986; Bytzer et al. 1986). The relapse rates were closely similar (64% in the antacid group and 57% in the H_2-receptor antagonist group). The relapse rates 6 months after initial healing with omeprazole (41 to 44%) or H_2-receptor antagonists (50 to 60%) are very similar (Bardhan et al. 1986; Hui et al. 1987; Lauritsen et al. 1985b; Maton 1991).

1.5 Does the Combination of an Antacid Plus an Anticholinergic Offer Any Advantage?

Before cimetidine was introduced, an antacid/anticholinergic combination was the prescriber's favourite, and the basis for the use of this combination was entirely empirical. A recent study (Strom et al. 1981) confirmed that the combination approach (7 doses of antacid per day with a total neutralising capacity of 600 mmol plus *l*-hyoscyamine 0.6mg twice a day) was superior to placebo and equivalent to cimetidine (1 g/day) in the healing of duodenal ulcer. Of high interest in this study is the observation that the time to relapse during the subsequent 12 months of follow-up was significantly *shorter* with cimetidine than with the antacid/anticholinergic combination, an observation also made independently by another group (Tomassetti et al. 1981). Since antacid alone does not differ from cimetidine in post-treatment relapse it would appear that the use of an anticholinergic may contribute to the longer remission.

1.6 Do Antacids Prevent Ulcer Recurrence?

Only 1 study has formally addressed this question. Antacid tablets (1 tablet 1 hour after meals and at bedtime; total acid neutralising capacity 100 mmol/day), were as effective and well tolerated as cimetidine 400mg every night as maintenance therapy for healed duodenal ulcer for a period up to 1 year (Bianchi Porro et al. 1986b). In a 24-month study, taking antacids only for pain relief was inferior to maintenance treatment with ranitidine, cimetidine or pirenzepine for the prevention of duodenal ulcer recurrence (Bresci et al. 1986). It appears on present evidence that multiple daily doses of antacids need be taken to prevent ulcer relapse. As a long term therapy, this is unlikely to meet with significant patient compliance.

2. How Do Antacids Work in Peptic Ulcer Disease?

2.1 Reduction of Postprandial Acid Secretion

In an *in vivo* study of 7 patients with duodenal ulcer (Fordtran et al. 1973), the rise in gastric acidity following a 150g meat meal disappeared when an antacid with 156 mmol of acid-neutralising capacity was given 1 hour after the meal. In fact, acidity was near zero (defined as pH ≥ 3.5) for 2 hours after ingestion of antacid. In another study of duodenal ulcer patients, 80 mmol antacid given 1 hour after a steak meal delayed the rise in gastric

acidity by 2 hours. A further dose of antacid given 3 hours after the meal delayed the rise by 3 hours (Fordtran 1973). Thus, with this regimen of 1- and 3-hour antacid administration, gastric acidity remains low for 4 hours after the meal.

Antacids given on an empty stomach have a much shorter duration of action (20 to 40 minutes) than if they are taken after a meal (Fordtran & Collyns 1966). It is also known that the water-insoluble, aluminium-magnesium antacids have a longer duration of buffering than sodium bicarbonate, probably because they leave the stomach more slowly with the solid portion of the meal (Simmons et al. 1986).

Thus, it is possible to reduce gastric acidity significantly during the day by using an intensive regimen, namely, an adequate dose of antacid given 1 and 3 hours after breakfast, lunch and supper. Indeed, a significant reduction in the amount of acid delivered to the duodenum after meals was achieved with antacid and was similar to that with cimetidine (Deering & Malagelada 1977).

2.2 Cytoprotection

Aluminium-containing antacids are cytoprotective because they protect gastric mucosa against various ulcerogenic and necrotising agents, including 0.6 mol/L HCl, 0.2 mol/L NaOH, and absolute alcohol (Gasbarrini et al. 1990; Tarnawski et al. 1990). Since gastric mucosal necrosis produced by absolute alcohol is independent of luminal acidity and cannot be eliminated by H_2-receptor antagonists, the protective mechanism of antacids must act other than by their acid-neutralising capacity. In fact, the protective mechanism is believed to be related to increase endogenous production of prostanoids and sulfhydryl-containing compounds (Gasbarrini et al. 1990; Szelenyi & Brune 1986).

Preclik et al. (1987) and Gasbarrini et al. (1990) demonstrated *in vivo* production of 6-keto prostaglandin (PG) $F_{1\alpha}$ (a stable metabolite of PGI_2) in the antrum in healthy volunteers and those with gastric antral ulcer after treatment with aluminium-containing antacid. The increase in this prostaglandin could enhance the gastric mucosal blood flow and hence resulting in a protective action. However, Szelenyi and Brune (1986), in their elegant experiments, further demonstrated in the rat model that pretreatment with a cyclo-oxygenase inhibitor (indomethacin) did not completely abolish the cytoprotective effect of aluminium-containing antacids. They showed that the endogenous gastric mucosal sulfhydryl-containing compounds also act as cytoprotective agents. This likely occurs via their effects as free radical scavengers and/or through their interaction with receptors involved in the release or mediation of action of gastric mucosal–damaging compounds.

2.3 Bile Acid Binding

Antacids are known to chelate conjugated bile. It has been speculated that antacids heal peptic ulcers by inactivation of the injurious effects of bile acids on the gastric mucosa (Clain et al. 1977). However, the theory remains unproven because there are no studies available to confirm peptic ulcer healing achievable solely by chelation of the noxious bile acids.

3. Gastro-Oesophageal Reflux Disease

GORD is very common among otherwise-healthy individuals. The exact prevalence of GORD has been based on guesses rather than facts. It has been estimated from a recent Gallup survey that >60 million people in the US have heartburn at least once a month and around 60% of these treat themselves with the over-the-counter antacid preparations (Sontag 1990).

Symptomatic GORD often manifests itself as heartburn, acid regurgitation or occasionally throat symptoms such as hoarseness, globus or dysphagia. When it is complicated by oesophagitis and/or ulceration it can precipitate odynophagia with or without dysphagia. The latter may indicate peptic stricture formation.

Diagnosis of GORD often relies on symptoms alone. However, it is well known that the degree of symptomatology may not correspond to the underlying oesophageal mucosal damage. Gastroscopy examination provides the best guide to the damage

sustained, particularly if biopsies are taken for histological examination. Ambulatory pH monitoring, however, yields more useful information about the frequency and severity of reflux, and may act as extremely valuable baseline for individuals with GORD. In combination with endoscopic findings, pH monitoring helps to determine appropriate medical treatment.

3.1 Medical Therapy for GORD

The aims of the medical therapy for GORD are to (a) provide effective symptomatic control of reflux symptoms, (b) promote healing of the mucosal lesions and (c) prevent relapse and complications. The treatment strategy depends on the degree and severity of symptoms and mucosal damage sustained.

3.2 Relief of Symptoms by Antacids

Antacids were the backbone of medical therapy for GORD until 1980s. A marketing survey (Graham et al. 1983) revealed that most antacids consumed in the US were taken to relieve reflux symptoms. Despite the frequency with which antacids are used in GORD, there have been few formal trials testing their efficacy. Behar et al. (1975) showed that symptomatic benefit occurred in mild oesophagitis. Graham and Patterson (1983) and Meyer et al. (1979) failed to demonstrate any difference between antacid and placebo. However, in 2 crossover studies by Grove et al. (1985) and Weberg and Berstad (1989), antacid was superior to placebo for symptomatic relief. Furthermore, antacid maintenance therapy after a successful course of treatment with H_2-receptor antagonist in erosive oesophagitis has provided adequate symptomatic control in a significant proportion of patients (Lieberman 1987).

3.3 Healing of Reflux Oesophagitis by Antacids

Antacids work in GORD probably as a result of a combination of acid neutralising ability, the inactivation of pepsin at high pH and bile acid-chelating effects. There are 3 reports (Castell & Levine 1971; Higgs et al. 1974; Malmud & Fisher 1978) showing that antacid increases lower oesophageal sphincter pressure and hence lowers the amount of gastro-oesophageal reflux. Up to 41% of patients with erosive oesophagitis were healed by antacid dosages as low as 30 mmol/day (Behar et al. 1978; Graham et al. 1977; McHardy 1978; Powell-Jackson et al. 1978; Saco et al. 1982; Sontag et al. 1987 Wesdorp et al. 1983).

There are conflicting reports about the efficacy of antacid-alginate compounds in the treatment of GORD. Some report superior effects (Barnardo et al. 1975; Beeley & Warner 1972; Chevrel 1980; Stanciu & Bennett 1974) and some show no difference from antacids (Graham et al. 1977; McHardy 1978). Like antacids, these compounds have been shown to reduce gastro-oesophageal reflux.

However, antacid or antacid-alginate compounds can only be used as adjuncts to antisecretory agents in the treatment of most patients with moderate or severe GORD. The efficacy of the H_2-receptor antagonists (average healing rate 70%) and the proton pump inhibitors (average healing rate 90%) in these patients has been established beyond doubt (Tytgat et al. 1990). Other agents such as carbenoxolone, sucralfate or prokinetic agents such as cisapride also provide better symptomatic relief and healing rates than antacid with or without alginate.

3.4 Recommendations

It is vital to give adequate explanation, appropriate advice on lifestyle modifications and recommend sensible usage of palatable antacid or antacid-alginate for symptomatic relief, particularly after meals and if heartburn occurs. These measures are often sufficient in the management of mild GORD. More troublesome GORD needs more potent medications, which can always be supplemented by on-demand antacid or antacid-alginate for breakthrough symptoms. The long term use of antisecretory drugs for moderately or severely affected individuals is effective and adverse effects are negligible. Alternative approaches such

as antireflux surgery should be considered in appropriate candidates.

4. Stress Ulcer Syndrome

Acute stress ulcer bleeding occurs in about 15% of critically ill patients nursed in present day intensive care units. Although the term 'stress ulcer' is used, it often embraces erosive haemorrhagic gastritis, which occurs frequently in this condition. The pathological features observed in patients with acute stress ulcer syndrome suggest a relationship between acid and ischaemia (Haglund 1990). There is a 3-fold increase in mortality in critically ill patients who have had a significant upper gastrointestinal bleed related to acute stress ulcer syndrome. Since the introduction of prophylactic treatment for acute stress ulcer, clinically overt bleeding from these lesions has reduced significantly to below 10% (Lam & Hui 1992).

4.1 Prophylactic Treatment for Acute Stress Ulcer Syndrome

Treatment regimens include the use of antacid titration by frequent administration to keep the gastric contents at neutral pH, H_2-receptor antagonists either by bolus injections or continuous infusion, and sucralfate suspension given intragastrically 4- or 6-hourly. Antacid titration that has met the pH goal (3.5 to 7.0) is just as effective as cimetidine in reducing the risk of bleeding from the stress ulcer (Zukerman & Shuman 1987). The overall success rate was >85% using either regimen. However, there was no reduction in mortality despite good results in reducing stress ulcer bleed.

On the other hand, sucralfate, according to recent reviews (Haglund 1990; Lam & Hui 1992), was superior to either antacid titration or H_2-receptor antagonists in preventing stress ulcer bleeding and nosocomial pneumonia, and reducing overall mortality. Sucralfate is a mucosal protective agent that possesses cytoprotective properties. It has recently been shown to enhance gastric mucosal blood flow, induce angiogenesis and have bactericidal effects. How much these effects contribute to the observed benefits in these patients can only remain speculative at this stage.

Antacid titration remains the best proven regimen for the prevention of stress ulcer bleeding, despite the drawback that it has not been shown to reduce mortality. Concomitant use of antibiotics to decolonise the stomach may theoretically reduce the nosocomial pneumonia rates, but whether the combination of antacid and antibiotics will eventually be shown to reduce mortality, as has been shown for sucralfate, will need further studies.

5. Pregnancy- and Delivery-Associated Reflux and Complications

GORD is estimated to be present in 30 to 50% of all pregnant women. The frequency increases from first to third trimester. It is believed that both mechanical and intrinsic (hormonal) factors are responsible for lowering the lower oesophageal sphincter pressure, resulting in GORD in pregnancy. The changes are reversible. Symptomatic patients are advised to avoid reflux-provoking postures, elevate the head of the bed, avoid food or fluid other than water within 3 hours of bedtime and use simple antacids whenever necessary.

No teratogenic effect of antacids has been observed in animal studies and they are therefore considered safe in pregnancy. Similarly, it is just as effective and safe to use H_2-receptor antagonists for patients with GORD if it does not respond to simple antacids (Calhoun 1992). Omeprazole, however, should not be used in pregnancy. Antacids can interfere with iron absorption, induce metabolic alkalosis and fluid overload both in the fetus and the mother, particularly if the bicarbonate products are used. Fortunately, most pregnant women respond to simple lifestyle modifications without resorting to any form of medications.

Acid aspiration syndrome (AAS) or Mendelson's syndrome accounts for a significant proportion of maternal mortality after caesarian section. This is likely to be attributed to reduced gastro-oesophageal sphincter pressure, recumbent position and anaesthetic agents. Gastric acid is the key

factor in determining the severity of aspiration pneumonitis.

Regular administration of mixture of magnesium trisilicate was until relatively recently recommended as the standard prophylactic therapy to prevent AAS. Taylor and Pryse-Davies demonstrated that neutralisation of gastric contents with a mixture of magnesium trisilicate to pH >2.5 prevented the severe pulmonary complications of acid aspiration (Taylor & Pryse-Davies 1966). Antacid remained the backbone prophylactic therapy against AAS until the mid-1980s. In 1984, a survey of 291 anaesthetic departments in the UK revealed that >50% of the units employed a mixture of magnesium trisilicate as the sole agent for the prophylaxis against AAS (Sweeney & Wright 1986).

However, its use has since declined significantly, so much so that another national survey done in 1989 of 288 obstetric anaesthetic units in the UK demonstrated that 80% of them had switched over to the combination of ranitidine and sodium citrate (Tordoff & Sweeney 1990). The use of magnesium trisilicate mixture alone was reduced from 53.5 to 8%.

The altered trend to the preference of anti-secretory drug over the antacid probably related to (a) the continuous reports of AAS despite adequate alkali administration (Moir 1980), (b) the experimental evidence that particulate antacids give rise to pneumonitis (Gibbs et al. 1979), (c) the poor compliance to 2-hourly antacid administration and (d) the proven efficacy of H_2-receptor antagonists in reducing gastric acidity. The occurrence of AAS in 8 of 9 patients despite adequate alkali administration (Moir 1980) obviously caused concern. It might suggest that alkali monotherapy may be an inadequate prophylaxis or that in a minority of cases it is ineffective in the recommended doses. Thus, the role of antacid monotherapy as prophylaxis against AAS has become very limited in recent years.

6. Miscellaneous Use of Antacids

6.1 Nonulcer Dyspepsia

Nonulcer dyspepsia is a heterogenous condition that can be subdivided into a number of symptomatic groups. These include patients with ulcer-like dyspepsia (typical symptoms of peptic ulcer are present), dysmotility (stasis)-like dyspepsia (symptoms include nausea, early satiety, bloating, and belching that suggest gastric stasis or small intestinal dysmotility), and reflux-like dyspepsia (heartburn or acid regurgitation in association with upper abdominal pain or discomfort). The underlying aetiology and pathogenesis of this condition remains poorly understood although it is likely to be a multifactorial disorder.

Table II. Advantages and disadvantages of antacid medications

Effect	Antacid/antacid-alginate	H_2-receptor antagonists	Omeprazole
Improves symptoms of reflux and dyspepsia	++	++	+++
Heals duodenal ulcer	++	++	+++
Heals gastric ulcer	+/–	+	++
Heals oesophagitis	+/–	+	+++
Prevents stress ulcer bleed	+	+	+/?
Ameliorates aspiration pneumonitis	+	++	+++
No (major) adverse effects	+	+	+/?
Good (or no) smell & taste	–	++	++
Simple to use	+	++	++
Inexpensive	+++	+	+

Symbols: +, ++, +++ = increasing the number of pluses denotes an increased degree of efficacy or advantage; – = not true; +/– = inconsistent results; ? = uncertain.

According to a previous nationwide survey by Tyllstrom and colleagues (1984), in Sweden 76% of the patients with nonulcer dyspepsia were empirically given a trial of antacid therapy, which was the most popular choice at the time. Subsequently, controlled clinical trials failed to show any significant benefit of antacids over placebo (Holcome et al. 1992; Nyren et al. 1986; Weberg & Berstad 1988). The management of this condition remains unsatisfactory. Until the underlying aetiology and pathogenesis of nonulcer dyspepsia has been clarified, it is impossible to make any recommendation for drug therapy.

6.2 Nonsteroidal Anti-Inflammatory Drug–Induced Upper Gastrointestinal Mucosal Damage

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to cause upper gastrointestinal mucosal damage. NSAID-induced ulcerations can be effectively treated by antacid therapy, like other non-NSAID peptic ulcerations, provided that the noxious agent is discontinued (Bianchi Porro & Lazzaroni 1993). Concomitant administration of NSAID with antacid may in some cases lead to delayed or reduced absorption of the NSAID (Verbeeck et al. 1983).

Although antacids are frequently and empirically prescribed along with NSAIDs for prophylaxis against NSAID-induced gastroduodenal mucosa injury, there has been no formal investigation with regards to their efficacy. However, an earlier study has shown that gastric microbleeding was reduced by coadministration of 'Maalox 70' with an NSAID (Domschke et al. 1986).

Misoprostol has become an established prophylactic agent for NSAID-induced gastric and duodenal ulcer (Lanza et al. 1988). H_2-receptor antagonists (Lanza et al. 1990; Robinson et al. 1991), omeprazole (Oddsson et al. 1992) and sucralfate (Lanza et al. 1988, 1990) appear to prevent the formation of NSAID-induced duodenal ulcer, which is not common, but not the formation of gastric ulcer induced by the NSAIDs.

7. Conclusions

Antacids with adequate acid-neutralising capacity have been shown beyond doubt to accelerate duodenal ulcer healing at a rate that is similar to that of H_2-receptor antagonists, but superior to that of placebo. Furthermore, they provide quick symptomatic relief of duodenal ulcer pain and are extremely inexpensive compared with H_2-receptor antagonists or proton pump inhibitors. The latter drugs undoubtedly have clear advantages (table II) over antacids in the modern day management of peptic ulcer disease. These potent acid suppressing agents are the preferred choices in the developed countries, where antacids can only adopt a supplementary role.

However, antacids may be the only affordable medication for the treatment of peptic ulcer disease in the third world or developing countries. In the management of gastro-oesophageal reflux disease in otherwise-healthy individuals and pregnant women, as well as in use as prophylactic agents in preventing stress ulcers, antacids still remain a viable option. Their use in nonulcer dyspepsia and NSAID prophylaxis, however, cannot be recommended.

References

Bardhan KD, Bianchi Porro G, Bose K, Daly M, Hinchliffe RFC, et al. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. Journal of Clinical Gastroenterology 8: 408-413, 1986

Barnardo DE, Lancaster-Smith M, Strickland ID, Wright JT. A double-blind controlled trial of Gaviscon in patients with symptomatic gastro-oesophageal reflux. Current Medical Research Opinion 3: 338-391, 1975

Beeley N, Warner JO. Medical treatment of symptomatic hiatus hernia with low-density compounds. Current Medical Research and Opinion 1: 63-69, 1972

Becker U, Lindorff K, Andersen C, Ranlov PJ. Antacid treatment of duodenal ulcer. Acta Medica Scandinavica 221: 95-101, 1987

Behar J, Brand DL, Brown FC, Castell DO, Cohen S, et al. Cimetidine in the treatment of symptomatic gastroesophageal reflux: a double-blind controlled trial. Gastroenterology 74: 441-448, 1978

Behar J, Sheahan DG, Biancani P, Spiro HM, Storer EH. Medical and surgical management of reflux esophagitis: a 38-month report on a prospective clinical trial. New England Journal of Medicine 293: 263-268, 1975

Berstad A, Rydning A, Aadland E, Kolstad B, Frislid K, et al. Controlled clinical trial of duodenal ulcer healing with antacid tablets. Scandinavian Journal of Gastroenterology 17: 953-959, 1982

Berstad A, Weberg R. Antacids in the treatment of gastroduodenal ulcer. Scandinavian Journal of Gastroenterology 21: 385-391, 1986

Bianchi Porro G, Lazzaroni M. Prevention and treatment of non-steroidal gastroduodenal lesions. European Journal of Gastroenterology & Hepatology 5: 420-432, 1993

Bianchi Porro G, Lazzaroni M, Pace F, Petrillo M. Long-term low-dose antacid versus cimetidine therapy in the treatment of duodenal ulcer recurrence. Scandinavian Journal of Gastroenterology 21: 1144-1146, 1986b

Bianchi Porro G, Parente F, Lazzaroni M, Baroni S, Panza E. Medium-dose antacids versus cimetidine in the short-term treatment of duodenal ulcer. Journal of Clinical Gastroenterology 8: 141-145, 1986a

Bresci G, Capria A, Federici G, Rindi G, Geloni M. Prevention of relapse with various antiulcer drugs. Scandinavian Journal of Gastroenterology 21 (Suppl. 121): 58-62, 1986

Brinton W. Lectures on diseases of the stomach, 2nd ed., Lea and Blanchard, Philadelphia, 1865

Bytzer P, Lauritsen K, Rask-Madsen J. Symptomatic recurrence of healed duodenal and prepyloric ulcers after treatment with ranitidine or high-dose antacid: a 1-year follow-up study. Scandinavian Journal of Gastroenterology 21: 765-768, 1986

Calhoun BC. Gastrointestinal disorders in pregnancy. Obstetric and Gynecological Clinicals of North America 19 (4): 733-744, 1992

Castell DO, Levine SM. Lower esophageal sphincter response to gastric alkalinization. A new mechanism for treatment of heartburn with antacids. Annals of Internal Medicine 74: 223-227, 1971

Chevrel B. A comparative crossover study in the treatment of heartburn and epigastric pain: liquid Gaviscon and magnesium-aluminium antacid gel. Journal of International Medical Research 8: 300-302, 1980

Clain JE, Malagelada JR, Chadwick VS. Binding properties in vitro of antacids for conjugated bile acids. Gastroenterology 73: 556-559, 1977

Coghlan JG, Gilligan D, Humphries H, McKenna D, Dooley C, et al. Campylobacter pylori and recurrence of duodenal ulcers - 12-months follow-up study. Lancet 2: 1109-1111, 1987

Cook PJ, Vincent-Brown A, Lewis SI, Perks, Jewell DP, et al. Carbenoxolone (Duogastrone) and cimetidine in the treatment of duodenal ulcer - a therapeutic trial. Scandinavian Journal of Gastroenterology 15 (Suppl. 65): 93-101, 1980

Crohn BB, Rosenak BD. An exhibition of books shown at the Graduate Fortnight illustrating the progress of gastroenterology. Bulletin of New York Academy of Medicine 11: 74, 1935

Deering TB, Malagelada J-R. Comparison of an H_2 receptor antagonist and a neutralising antacid on postprandial acid delivery into the duodenum in patients with duodenal ulcer. Gastroenterology 73: 11-14, 1977

Domschke W, Agel J, Ruppin H, Kaduk B. Antacid protection of gastric mucosa. Klinische Wochenschrift 64 (Suppl. 7): 28-31, 1986

Drake D, Hollander D. Neutralizing capacity and cost effectiveness of antacids. Annals of Internal Medicine 94: 215-217, 1981

Faizallah R, De Haan HA, Krasner N, Walker RJ, Morris AI, et al. Is there a place in the United Kingdom for intensive antacid treatment for chronic peptic ulceration? British Medical Journal 289: 869-871, 1984

Fedeli G, Anti M, Rapaccini GL, De Vitis I, Butti A, et al. A controlled study comparing cimetidine treatment to an intensive antacid regimen in the therapy of uncomplicated duodenal ulcer. Digestive Diseases and Sciences 24: 758-762, 1979

Fordtran JS. Reduction of acidity by diet, antacids and anticholinergic agents. In Sleisenger & Fordtran (Eds) Gastrointestinal diseases, 1st ed., pp. 718-742, WB Saunders, Philadelphia, 1973

Fordtran JS, Collyns JAH. Antacid pharmacology in duodenal ulcer: effects of antacids on postcibal gastric acidity and peptic activity. New England Journal of Medicine 274: 921-927, 1966

Fordtran JS, Morawski SG, Richardson CT. In vivo and in vitro evaluation of liquid antacids. New England Journal of Medicine 288: 923-928, 1973

Gasbarrini G, Andreone P, Baraldini M, Cursaro C, Micaletti E. Antacids in gastric ulcer treatment: evidence of cytoprotection. Scandinavian Journal of Gastroenterology 25 (Suppl. 174): 44-47, 1990

Gibbs CP, Schwartz DJ, Wynne JW, Hood CI, Kuck EJ. Antacid pulmonary aspiration in the dog. Anesthesiology 51: 380-385, 1979

Graham DY, Lanza F, Dorsh ER. Symptomatic reflux oesophagitis: a double-blind controlled comparison of antacids and alginate. Current Therapeutic Research 22: 653-658, 1977

Graham DY, Patterson DJ. Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. Digestive Diseases Science 28: 559-563, 1983

Graham DY, Smith JL, Patterson DJ. Why do apparently healthy people use antacid tablets? American Journal of Gastroenterology 78: 257-260, 1983

Grove O, Bekker C, Jeppe Hansen NG. Ranitidine and high-dose antacid in reflux oesophagitis. Scandinavian Journal of Gastroenterology 20: 457-461, 1985

Haglund U. Stress ulcers. Scandinavian Journal of Gastroenterology 25 (Suppl. 175): 27-33, 1990

Higgs RH, Smith RD, Castell DO. Gastric alkalinization: effect on lower esophageal sphincter pressure and serum gastrin. New England Journal of Medicine 291: 486-488, 1974

Holcombe C, Thom C, Kaluba J, Lucas SB. Helicobacter pylori clearance in the treatment of non-ulcer dyspepsia. Alimentary Pharmacology and Therapeutics 6: 119-123, 1992

Hollander D, Harlan J. Antacids vs placebos in peptic ulcer therapy: a controlled double-blind investigation. Journal of the American Medical Association 226: 1181-1185, 1973

Hui WM, Lam SK, Lau WY, Branicki FJ, Lai CL, et al. Omeprazole (OME) vs ranitidine (RAN) for duodenal ulcer (DU) - one-week, low-dose regimens and factors affecting healing. Abstract. Gastroenterology 92: 1443, 1987

Ippoliti AF, Sturdevant RAL, Isengerg JI, Binder M, Camacho R, et al. Cimetidine versus intensive antacid therapy for duodenal ulcer. A multicenter trial. Gastroenterology 74: 393-395, 1978

Isenberg JI, Peterson WL, Elashoff JD, Sandersfeld MA, Reedy TJ, et al. Healing of benign gastric ulcer with low-dose antacid or cimetidine: a double-blind, randomized, placebo-controlled trial. New England Journal of Medicine 308: 1319-1324, 1983

Kumar N, Vij JC, Karol A, Anand BS. Controlled therapeutic trial to determine the optimum dose of antacids in duodenal ulcer. Gut 25: 1199-1202, 1984

Lam SK. Antacids: past, present and future. In Piper (Ed.) Peptic ulcer. Clinics in gastroenterology. Vol. 2, pp. 641-654, WB Saunders, London, Philadelphia, Toronto, 1988

Lam SK. Academic investigator's perspectives of medical treatment for peptic ulcer. In Swabb & Szabo (Ed.) Ulcer disease: investigation and basis for therapy, pp. 431-450, Marcel Dekker, New York, 1991

Lam SK, Hui WM. Is stress ulcer bleeding still an obnoxious killer in present day ICU? Journal of Hepatology and Gastroenterology 7: 553-555, 1992

Lam SK, Hui WM, Lau WY, Branicki FJ, Lai CL, et al. Sucralfate overcomes adverse effect of cigarette smoking on duodenal ulcer

healing and prolongs subsequent remission. Gastroenterology 92: 1193-1201, 1987

Lam SK, Hui WM, Ng MMT. The stomach. In Gitnick GL (Ed.) Current gastroenterology, pp. 31-65, Yearbook Medical Publishers, Chicago, London, 1987

Lam SK, Lam KC, Lai CL, Yeung CK, Yam LYC, et al. Treatment of duodenal ulcer with antacid and sulpiride: a double-blind controlled study. Gastroenterology 76: 315-322, 1979

Lanza FL, Graham DY, Davis DE, Rack MF. Endoscopic comparison of cimetidine and sucralfate for prevention of naproxen-induced acute gastroduodenal injury: effect of scoring method. Digestive Diseases and Sciences 35: 1494-1499, 1990

Lanza FL, Peace K, Gustitus L, Rack MF, Dickson B. A blinded endoscopic comparative study of misoprostol versus sucralfate and placebo in the prevention of aspirin-induced gastric and duodenal ulceration. American Journal of Gastroenterology 83: 143-146, 1988

Lauritsen K, Bytzer P, Hansen J, Bekker C, Rask-Madsen J. Comparison of ranitidine and high-dose antacid in the treatment of prepyloric or duodenal ulcer: a double-blind controlled trial. Scandinavian Journal of Gastroenterology 20: 123-128, 1985a

Lauritsen K, Rune SJ, Bytzer P, Kelbaek H, Jensen KG, et al. Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. New England Journal of Medicine 312: 958-961, 1985b

Lieberman DA. Medical therapy for chronic reflux esophagitis: long term follow-up. Archives of Internal Medicine 147: 1717-1720, 1987

Lux G, Hentschel H, Rohner HG, Brunner H, Schutze K, et al. Treatment of duodenal ulcer with low-dose antacids. Scandinavian Journal of Gastroenterology 21: 1063-1068, 1986

Malmud LS, Fisher RS. Quantitation of gastro-esophageal reflux before and after therapy using the gastroesophageal scintiscan. South Medical Journal 71: 10, 1978

Martin DF, Hollanders D, May SJ, Ravenscroft MM, Tweedle DE, et al. Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. Lancet 1: 7-10, 1981

McHardy G. A multicentric, randomized clinical trial of Gaviscon in reflux. South Medical Journal 71: 16-21, 1978

McIntosh JH, Byth K, Piper DW. Environmental factors in aetiology of chronic gastric ulcer: a case control study of exposure variables before the first symptoms. Gut 26: 789-798, 1985

Meyer C, Berenweig H, Kuljian B, Callachan C, McCallum RW, et al. Controlled trial of antacid (AA) versus placebo (P) on relief of heartburn. Gastroenterology 76: 1201 (abstract), 1979

Moir D. Maternal mortality and anaesthesia. British Journal of Anaesthesia 52: 1-3, 1980

Nyren O, Adami HO, Bates S, Bergstrom R, Gustavsson S, et al. Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. New England Journal of Medicine 314: 339-343, 1986

Oddsson E, Jonsson H, Thjodleifsson B. Comparison between ranitidine and omeprazole for protection against gastroduodenal damage caused by naproxen. Scandinavian Journal of Gastroenterology 27: 1045-1048, 1992

Pace F, Broker HJ, Caspary W, Feurle G, Fimmel CJ, et al. Therapy of stomach ulcer with low-dose antacid gel and cimetidine: a multicenter double-blind study. Deutsche Medizinische Wochenschrift 22: 283-287, 1985

Peterson WL, Sturdevant RAL, Frankl HD, Richardson CT, Isengern JI, et al. Healing of duodenal ulcer with an antacid regimen. New England Journal of Medicine 297: 341-345, 1977

Pickering GW. Abdominal pain. In Jones FA (Ed.) Modern trends in gastroenterology. Vol 1, Chap. 4, Butterworths, London, 1952

Powell-Jackson P, Barkley H, Northfield TC. Effect of cimetidine in symptomatic gastro-oesophageal reflux. Lancet 2: 1068-1069, 1978

Preclik G, Stange EF, Gerber K, Fetzer G, Horn H, Ditschuneit H. Stimulation of endogenous prostaglandin synthesis by antacids in human gastric and duodenal mucosa. Gastroenterology 92: 1579, 1987

Robinson M, Mills RJ, Euler AR. Ranitidine prevents duodenal ulcers associated with non-steroidal anti-inflammatory drug therapy. Alimentary Pharmacology & Therapeutics 5: 143-150, 1991

Rydning A, Weberg R, Lange O, Berstad A. Healing of benign gastric ulcer with low-dose antacids and fiber diet. Gastroenterology 91: 56-61, 1986

Saco LS, Orlando RC, Levinson SL, Bozymski EM, Jones JD, et al. Double-blind controlled trial of bethanechol and antacid versus placebo and antacid in the treatment of erosive esophagitis. Gastroenterology 82: 1369-1373, 1982

Schwarz K. Ueber penetrierende Magen-und Jejunalgesch wure. Beitrage zur Klinische Chirurgie 67: 95, 1910

Simmons TC, Hogan DL, Selling JA, Maxwell V, Isenberg JI. The effect of sodium bicarbonate versus aluminum-magnesium hydroxide on postprandial gastric acid in duodenal ulcer patients. Journal of Clinical Gastroenterology 8: 146-149, 1986

Sippy BW. Gastric and duodenal ulcers, medical cure by an efficient removal of gastric juice corrosion. Journal of American Medical Association 64: 1625, 1915

Sontag SJ. The medical management of reflux esophagitis. Gastroenterology Clinics of North America 19: 683-712, 1990

Sontag S, Robinson M, McCallum RW, Barwick KW, Nardi R. Ranitidine therapy for gastroesophageal reflux disease: results of a large double-blind trial. Archives of Internal Medicine 147: 1485-1491, 1987

Stanciu C, Bennett JR. Alginate-antacid in the reduction of gastro-oesophageal reflux. Lancet 1: 109-111, 1974

Strom M, Gotthard R, Bodemar G, Walan A. Antacid/anticholinergic, cimetidine and placebo in the treatment of active peptic ulcers. Scandinavian Journal of Gastroenterology 16: 593-602, 1981

Sweeney BP, Wright I. The use of antacids as a prophylaxis against Mendelson's syndrome in the United Kingdom. Anaesthesia 41: 419-422, 1986

Szelenyi I, Brune K. Possible role of sulfhydryls in mucosal protection induced by aluminium hydroxide. Digestive Diseases and Sciences 31: 1207-1210, 1986

Tarnawski A, Hollander D, Gergely H. Antacids: new perspectives in cytoprotection. Scandinavian Journal of Gastroenterology 25 (Suppl. 174): 9-14, 1990

Taylor RG, Pryse-Davies J. The prophylactic use of antacids in the prevention of the acid-pulmonary aspiration syndrome (Mendelson's syndrome). Lancet 1: 288-291, 1966

Tomassetti P, Stanghellini E, Bonorag G, Vezzadini P, Labo G. Comparative trial on healing and relapse of duodenal ulcer treated with trithiozine or cimetidine. Current therapeutic Research 29: 517-524, 1981

Tordoff SG, Sweeney BP. Acid aspiration prophylaxis in 288 obstetric departments in the United Kingdom. Anaesthesia 45: 776-780, 1990

Tyllstrom J, Adami HO, Agenas I, Gustavsson S, Loof L, et al. The clinical diagnosis of gastritis II: aspects of current therapy and drug consumption. Scandinavian Journal of Gastroenterology 19: 755-760, 1984

Tytgat GNJ, Nio CY, Schotborgh RH. Reflux esophagitis. Scandinavian Journal of Gastroenterology 25 (Suppl. 175): 1-12, 1990

Verbeeck RK, Blackburn JL, Loewen GR. Clinical pharmacokinetics of non-steroidal anti-inflammatory drugs. Clinical Pharmacokinetics 8: 297-331, 1983

Weberg R, Berstad A. Low-dose antacids and pirenzepine in the treatment of patients with non-ulcer dyspepsia and erosive prepyloric changes: a randomised, double-blind, placebo-controlled trial. Scandinavian Journal of Gastroenterology 23: 237-243, 1988

Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. Scandinavian Journal of Gastroenterology 24: 401-406, 1989

Weberg R, Berstad A, Lange O, Schultz T, Aubert E. Duodenal ulcer healing with four antacid tablets daily. Scandinavian Journal of Gastroenterology 20: 1041-1045, 1985

Weberg R, Aubert E, Dahlberg O, Dybdahl J, Ellekjaer E, et al. Low dose antacids or cimetidine for duodenal ulcer? Gastroenterology 95: 1465-1469, 1988

Wesdorp ICE, Dekker W, Klinkenberg-Knol EC. Treatment of reflux oesophagitis with ranitidine. Gut 24: 921-924, 1983

Zuckerman GR, Shuman R. Therapeutic goals and treatment options for prevention of stress ulcer syndrome. American Journal of Medicine 83 (Suppl. 6A): 29-35, 1987

Correspondence and reprints: Prof *S.K. Lam*, Division of Gastroenterology and Hepatology, Queen Mary Hospital, Pokfulam, Hong Kong.

0022-5282/94/3604-0541$03.00/0
THE JOURNAL OF TRAUMA

Vol. 36, No. 4
Printed in U.S.A.

COMPARISON OF ACID NEUTRALIZING AND NON-ACID NEUTRALIZING STRESS ULCER PROPHYLAXIS IN THERMALLY INJURED PATIENTS

William G. Cioffi, MD, FACS, Albert T. McManus, PhD, Loring W. Rue, III, MD, FACS,* Arthur D. Mason, MD, William F. McManus, MD, FACS, and Basil A. Pruitt, Jr., MD, FACS

We have compared the effectiveness of non-acid neutralizing stress ulcer prophylaxis (SUC) with sucralfate (n = 48) with that of acid neutralizing prophylaxis (AN) utilizing antacids and cimetidine (n = 48) in the prevention of stress ulcer bleeding and nosocomial pneumonia (PN) in thermally injured patients. In the subset of intubated patients, the incidence of PN was 17.8% and 42.8% in the AN and SUC groups, respectively ($p < 0.05$) despite a similar postburn time of onset of pneumonia. Ten patients in each group died. Three patients in the SUC group developed upper GI bleeding with one requiring gastrectomy. Bacterial colonization of the upper airway occurred in virtually all patients, whereas 83% (SUC) and 96% (AN) had colonization of gastric contents. Gram-negative colonization rates for the upper airway were not different (70%) whereas 48% of SUC patients compared with 60% of AN patients had gram-negative gastric colonization. In conclusion, SUC therapy was efficacious in the prevention of stress ulcer bleeding but did not alter the rate of bacterial colonization of the airway or gastric contents, and was associated with a higher incidence of nosocomial pneumonia in intubated patients.

BEFORE THE ADOPTION of measures to neutralize gastric acid, gastrointestinal bleeding was a common and lethal complication in thermally injured patients. Endoscopically documented mucosal ulcerations could be identified in up to 90% of patients with burns of 35% or more of the body surface, and in up to one quarter of these patients clinically important bleeding occurred that was associated with mortality rates of 50% to 70%.[1-3] Therapy aimed at maintaining gastric pH above 4.5 virtually eliminated this complication.[4,5]

Neutralization of gastric acid allows the stomach contents to become rapidly colonized with bacteria, principally gram-negative organisms. In 1978, Atherton and White proposed that the stomach might serve as a reservoir for bacteria that subsequently colonized and infected the respiratory tracts of mechanically ventilated patients.[6,7] Recent reports have suggested that stress ulcer prophylaxis that does not result in gastric alkalinization may decrease the risk of nosocomial pneumonia, principally by decreasing gastric bacterial colonization.[8-11]

Nosocomial pneumonia is the most frequent life-threatening infection that occurs in thermally injured patients. Pulmonary infection was responsible for 42% of deaths that occurred in our burn center between 1987 and 1991.[12] In the past we have identified that the major risk factors for the development of pulmonary infection are the presence of inhalation injury requiring mechanical ventilatory support, age, and extent of burn.[13] Some authors suggest that standard stress ulcer prophylaxis regimens that neutralize gastric acid should be added to this list.[14]

The current study was designed to compare the efficacy of non-acid neutralizing stress ulcer prophylaxis using sucralfate with that of conventional acid neutralizing therapy in the prevention of stress ulcer-induced GI bleeding and nosocomial pneumonia in critically ill, thermally injured patients.

PATIENTS AND METHODS

Study Design

All adult burn patients (18 year old)admitted to the United States Army Institute of Surgical Research within 48 hours of injury with greater than a 20% total body surface area burn were considered for entry into this study. Patients with a prior history of peptic ulcer disease, preinjury H_2 receptor antagonist therapy, or a diagnosis of pneumonia at the time of admission

From the U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas.
* Current address: Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama 35294.
Presented at the Fifty-third Annual Session of the American Association for the Surgery of Trauma, September 23-25, 1993, New Orleans, Louisiana.
The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense.
Address for reprints: Library Branch, U.S. Army Institute of Surgical Research, Fort Sam Houston, TX 78234.

were excluded from enrollment. Consecutive patients were randomized in a pairwise fashion to receive either acid neutralizing stress ulcer prophylaxis consisting of cimetidine and antacids (AN) or non-acid neutralizing therapy using sucralfate (SUC). Cimetidine was administered every 6 hours at a dose of 300 mg. The dose was subsequently adjusted depending upon patients' renal function and gastric pH. Antacids were administered as a 30-mL bolus orally or via nasogastric tube every 2 hours. Gastric pH was measured every hour using pH paper or an indwelling gastric pH probe (both were calibrated against reference standards) and if the pH was less than 4.5, the dose of antacids was doubled or administered on an hourly basis. If this failed to increase gastric pH above the threshold level, the cimetidine administration was changed to a continuous infusion. Sucralfate, 1 g suspended in 20 mL of water, was administered orally or via nasogastric tube every 6 hours. The tube was clamped for 1-hour following administration.

All patients were resuscitated using the modified Brooke formula. Inhalation injury was diagnosed by bronchosopy or xenon ventilation/perfusion scanning. Wound care consisted of alternating silver sulfadiazine and mafenide acetate with excision and grafting initiated within the first postburn week. Continuous enteral feedings were begun on postburn day 3 at a rate sufficient to meet peak metabolic demands if the patient was unable to meet requirements orally.

All patients with gross clinically evident upper GI bleeding underwent endoscopy to verify the source of bleeding. Evidence of clinically apparent stress ulceration was considered a treatment failure.

Infectious Complications

The diagnosis of pneumonia was based upon roentgenographic findings consistent with pneumonia, sputum leukocytosis greater than 25 white cells per high-power microscopic field, and growth of a predominant organism on sputum sample culture. Chest roentgenograms were reviewed by a staff surgeon and a radiologist who were unaware of the patient's treatment group. Gram's staining and cultures of sputum samples and gastric aspirate cultures were obtained every Monday, Wednesday, and Friday, and as clinically dictated. The isolates from each source were typed and compared. The timing of colonization for each source was recorded.

Data Analysis

The age, total body surface area burned, presence of inhalation injury, requirement for intubation and ventilatory support, length of intubation, presence of pneumonia, postburn day of diagnosis of pneumonia, and outcome were recorded for all patients. All data are presented as the mean ± standard error of the mean, and were analyzed by Chi-square or unpaired Student's *t* test when appropriate. Logistic regression analysis was performed to identify the factors associated with the development of pneumonia or mortality. All analyses were performed using the BMDP statistical package.

RESULTS

From March 1990 through December 1992, 100 patients were randomized into this study, with 50 receiving acid neutralizing therapy and 50 non-acid neutralizing prophylaxis. There were two protocol violations in each group, leaving a total of 96 patients for evaluation. Demographic data are displayed in Table 1. There were no significant differences in age, burn size, the presence of inhalation injury, requirements for intubation, or outcome between the two groups. The groups were compared using a severity index based upon age, burn size, and the presence of inhalation injury.[13] The severity findings were not different between groups, indicating the similarity of the patient cohorts.

Table 1
Patient cohorts

	Acid Neutralizing Treatment (n = 48)	Sucralfate Treatment (n = 48)
Age (years)	37.6 ± 2.5	36.7 ± 1.99
TBSA (%)	49.3 ± 2.9	46.5 ± 3.5
Inhalation injury	22 (45%)	27 (56%)
Intubation	29 (60%)	28 (58%)
Mortality (%)	20.8	20.8
Severity index	28.28	33.37

TBSA = Total body surface area burned.

Table 2
Inhalation injury patients

	Acid Neutralizing Treatment (n = 22)	Sucralfate Treatment (n = 27)
Age (years)	40.8 ± 4.1	36.3 ± 2.3
TBSA (%)	50.6 ± 4.4	60.3 ± 4.6
Intubation	20 (91%)	22 (81.4%)
Mortality (%)	27.2	29.6
Severity index	45.63	50.96

TBSA = Total body surface area burned.

Table 3
Intubated patients

	Acid Neutralizing Treatment (n = 29)	Sucralfate Treatment (n = 28)
Age (years)	40.1 ± 3.7	36.4 ± 2.5
TBSA (%)	54 ± 4.1	63 ± 4.2
Inhalation injury	21 (72%)	22 (78.5%)
Mortality (%)	27.6	32
Severity index	45.66	55.02

TBSA = Total body surface area burned.

Since both the presence of inhalation injury and the requirement for intubation are significant risk factors for the development of nosocomial pneumonia, patients were further segregated based upon these two factors. Tables 2 and 3 contain the demographic data for patients in each cohort segregated by their prophylaxis regimens. There were no discernible differences between groups in each cohort. In the intubated cohort, the severity indices of 0.4566 and 0.5502 for AN and SUC, respectively, were not significantly different since the 95% confidence limits overlapped.

Clinically apparent upper gastrointestinal tract bleeding developed in three patients receiving sucralfate and in no patients receiving AN. One patient in the sucralfate group required a gastrectomy for control of hemorrhage.

Pneumonia occurred at a greater frequency in the

sucralfate group compared with the acid neutralizing group, although the difference was not statistically significant (Table 4). This same trend persisted in the inhalation injury and intubation cohorts. Of particular note was the incidence of pneumonia that occurred while patients were intubated: 42.8% of the sucralfate group and 17.9% of the acid neutralizing group developed pneumonia while intubated, a difference that was statistically significant. The PBD of diagnosis of pneumonia was identical between the two groups: 23.3 ± 10 days in AN and 23.8 ± 6.8 days in the sucralfate group. Not surprisingly, the duration of intubation was longer in the sucralfate group, presumably related to the higher incidence of pneumonia (13.5 ± 2.5 days vs. 22.3 ± 5.2 days). The types of organisms causing pneumonia in each group are shown in Table 5. Although SUC treatment tended to have a higher proportion of gram-positive pneumonias compared with AN treatment, this difference was not statistically significant.

The percentages of patients in each group who developed positive sputum or gastric cultures for any bacteria, and gram-negative bacteria specifically, are shown in Table 6. The incidence of sputum colonization was identical between the two groups, whereas there was a small but not significant decrease in gastric colonization rates in the sucralfate group compared with the acid neutralizing group. The postburn day of colonization of the sputum samples for any bacteria and gram-negative bacteria specifically in AN and SUC were not statistically difference (1.7 ± 0.2 days vs. 1.89 ± 0.35 days, and 7.73 ± 2.5 days vs. 9.36 ± 3.7 days, respectively). The postburn day of intragastric colonization was nearly identical, although the postburn day of gram-negative colonization was nearly twice that in the sucralfate group compared with the acid-neutralizing group (2.02 ± 0.22 days vs. 2.89 ± 0.78 days and 4.1 ± 0.49 days vs. 7.26 ± 1.5 days, respectively).

The highest and lowest gastric pH values were recorded each day in all patients. The mean high gastric pH was 7.11 ± 0.3 and 5.77 ± 0.4 in the AN and SUC groups, respectively. The mean low gastric pH was 3.74 ± 0.6 and 3.03 ± 0.1 in the AN and SUC groups, respectively. Hourly gastric pH was recorded in 13 AN patients and six SUC patients. In the AN group, 18% of the readings were less than 4.0. Surprisingly, only 36% of the SUC readings were less than 4.0, despite the lack of acid neutralization therapy.

There were nine deaths before postburn day 5: five in the acid-neutralizing group and four in the sucralfate group. None of these patients developed pneumonia. In general, these were patients with large burns and severe inhalation injuries who did not live long enough to be at risk for the development of pneumonia. Exclusion of these patients from analysis did not alter the above findings.

Table 7 compares the patients with and without pneumonia irrespective of their prophylaxis regimen. Patients who died before postburn day 5 were excluded from this analysis, because none of these patients developed pneumonia, and the PBD of death was significantly earlier than the mean postburn day of diagnosis of pneumonia. As expected, the patients who developed pneumonia were older ($p = 0.07$), had larger burns ($p < 0.0001$), and had a higher incidence of inhalation injury ($p < 0.001$) and intubation ($p < 0.01$). Although mortality was greater in

Table 4
Incidence of pneumonia

	Acid Neutralizing Treatment	Sucralfate Treatment
All patients	18.7% (9)	35.4% (17)
Inhalation injury		
Yes	31.8% (7/22)	48% (13/27)
No	7.5% (2/26)	19% (4/21)
Intubated		
Yes	28% (8/29)	57% (16/28)
No	5.3% (1/19)	5% (1/20)
While intubated	17.9% (5/29)	42.8% (12/28)*

* $p < 0.05$.

Table 5
Type of pneumonia

	Acid Neutralizing Treatment	Sucralfate Treatment
Gram positive	11% (1)*	29% (5)
Gram negative	33% (3)	12% (2)
Mixed	56% (5)	59% (10)

* Number of patients in parentheses.

Table 6
Colonization rates (%)

	Acid Neutralizing Treatment	Sucralfate Treatment
Sputum		
Any	100	98
Gram-negative	70	70
Gastric		
Any	96	83
Gram negative	60	48

Table 7
Comparison of patients without and with pneumonia

	No (n = 61)	Yes (n = 26)
Age (years)	34.3 ± 1.8	40.2 ± 2.7
Total body surface area burned (%)	38.5 ± 2.3	59.7 ± 3.8*
Inhalation injury (%)	39.3	76.9*
Intubation (%)	39.3	92.3*
Length of intubation (days)†	12.1 ± 2.6	29.1 ± 5.5*
Length of intubation before pneumonia (days)	—	10.9 ± 1.9
Mortality (%)	9.8	19.2

* $p < 0.05$ compared with no pneumonia.
† Mean ± SEM only for intubated patients.

these patients the difference was statistically significant, possibly secondary to a type II error.

A stepwise logistic regression analysis was performed to determine which factors were correlated with the development of pneumonia. That analysis revealed that increasing patient age and extent of burn as well as the requirement for intubation were independently associated with the development of pneumonia, whereas the presence of inhalation injury and the type of stress ulcer prophylaxis therapy were not. Logistic regression analysis was also performed to identify the factors associated with a fatal outcome. Not surprising, age, extent of burn, and the development of pneumonia were significant predictors of death, whereas intubation, inhalation injury, and type of stress ulcer prophylaxis were not.

DISCUSSION

Thermally injured patients represent a population at significant risk for the formation of gastric stress ulcers. In 1974 Czaja and colleagues reported that gastric mucosal lesions can form within minutes to hours following injury, and that the incidence approaches 100% in patients with serious burns.[1] Before the institution of prophylactic therapy, clinical complications occurred in 28% of patients, with 13% requiring surgical intervention. The recognition that acid was a prerequisite for the development of gastric mucosal injury led to the initiation of antacid therapy for prophylaxis.[4] The advent of histamine H_2 receptor antagonists added another option and these agents, either alone or in combination, have significantly reduced the incidence of stress ulcers to less than 2% of all burn patients.[15]

Those data led to the institution of our current regimen for prophylaxis consisting of both antacid and H_2 antagonist therapy. The success of this approach requires assiduous titration of gastric pH to greater than 4.5. Failure to achieve pH control when using acid neutralization prophylaxis leads to an unacceptable rate of upper GI bleeding, as documented by Laggner et al.[16] In their study, failure to increase gastric pH using bolus infusions of ranitidine resulted in a 43.7% incidence of bleeding in a group of patients requiring long-term ventilation. Such a treatment regimen is labor intensive, exposes caregivers to patient secretions, and results in an unacceptable level of side effects if either agent is employed alone. In our experience, the side effects associated with the use of these agents may be limited by the simultaneous use of both, thus decreasing the necessary dose of each.

Despite this success, such a regimen recently has been implicated as unnecessarily exposing patients to an increased risk of nosocomial pneumonia.[17,18] In light of that possibility and the diminishing incidence of stress ulcers some have suggested that prophylaxis is unnecessary.[19,20] Although not specifically addressed in our study, two meta-analyses have clearly demonstrated that acid neutralization prophylaxis significantly decreases the incidence of gastric bleeding in both surgical and medical ICU patients compared with placebo therapy.[21,22] Thus it is clear that some form of prophylaxis is appropriate. It is unquestioned that maintaining the intragastric pH greater than 4.5 results in bacterial colonization of stomach contents.[23,24] The hypothesis that such overgrowth leads to an increased incidence of nosocomial pneumonia prompted a search for an alternative method of stress ulcer prophylaxis that did not alter gastric pH. Sucralfate, a chemical complex of sucrose octosulfate and aluminum hydroxide, appears to protect against stress ulceration through pepsin absorption, mucosal protein binding, and cytoprotection, presumably via increased local prostaglandin production, without significantly altering gastric pH.[25,26] Hypothetically, such a compound should reduce the incidence of nosocomial pneumonia by decreasing colonization of gastric contents.

In 1987 Tryba compared sucralfate with antacid prophylaxis in a series of surgical ICU patients requiring mechanical ventilation and found a threefold greater incidence of pneumonia in the patients receiving antacids.[9] In that same year, Driks et al. reported that sucralfate-treated patients had a lower incidence of nosocomial pneumonia than patients treated with either antacids or H_2 antagonists alone or in combination.[8] However, when the latter study is carefully examined, only patients treated with antacids had a higher incidence of pneumonia. Since 1987 there have been multiple studies comparing various regimens of non-acid neutralizing prophylaxis with acid neutralizing regimens. Many of these studies have similar shortcomings in that heterogeneous patient populations with relatively small numbers of patients were studied.[11,27] Indeed, two recent meta-analyses have offered conflicting conclusions as to which type of regimen is superior.[28,29] It is probable that the conflict between the two meta-analyses can be explained by the combining of trials involving heterogeneous patient groups with poorly matched patient cohorts in which many different prophylaxic regimens were employed. In a recent well controlled, randomized prospective trial comparing sucralfate with either bolus or continuous cimetidine administration in nonburned trauma patients, Fabian et al. found no difference in the incidence of nosocomial pneumonia.[30]

Our study represents a relatively homogeneous patient population in which the severity of the precipitating insult can be easily indexed, i.e., extent of burn and the presence or absence of inhalation injury. In this patient population, sucralfate prophylaxis did not result in a lower incidence of nosocomial pneumonia but, in fact, in the patients requiring intubation, was associated with a higher incidence of pneumonia during the period of ventilatory support. Fabian and colleagues indicted antacid prophylaxis as the agent responsible for the increase in nosocomial pneumonia reported in some series and thus their trial of cimetidine versus sucralfate would not have been expected to show any difference.[30] In our trial, as

in that of Simms and colleagues,[31] this was not found to be true. In both studies, antacids were not associated with an increase in the frequency of pneumonia. Furthermore, although acid neutralization appears to hasten gastric colonization with gram-negative bacteria, no association with frequency of organism-specific pneumonia could be identified. The absence of a relationship between gastric colonization and subsequent tracheal colonization and nosocomial pneumonia has also been reported in postoperative neurosurgical patients receiving ranitidine and antacids as well as a group of ventilated general ICU patients receiving selective gut decontamination.[23,24]

In an attempt to reconcile the conflicting literature, Tryba and colleagues have reviewed many of the recently published studies.[14] They concluded that since only some populations are at risk for the development of nosocomial pneumonia via the gastropulmonary route only they would benefit from non-acid neutralizing prophylaxis regimens. Such groups consist of surgical and trauma patients, patients receiving anti-ulcer prophylaxis for more than 7 days, patients receiving high-dose antacid therapy with pH titration, patients receiving continuous enteral nutrition, and patients requiring mechanical ventilation for more than 4 days. Other high-risk groups consist of patients with a pneumonia rate that exceeds 20% and those with an increase in gastric colonization during acid neutralization therapy. Our patient population meets the majority of these criteria, and yet we found no benefit from the use of non-acid neutralizing therapy. Moreover, recent reports impugn several of the proposed criteria. First, two recent studies in trauma patients have shown early continuous enteral nutrition to result in a lower, not higher, incidence of both pulmonary and total infectious complications.[32,33] Second, Simms' study clearly showed a higher incidence of gastric colonization but no resultant increase in pneumonia rates when acid neutralizing prophylaxis was employed.[31]

In a recent communication, Tryba redefined the "high-risk" factors, to include "surgical patients receiving long-term mechanical ventilation and those with low basic pH and no continuous enteral feedings."[34] Our limited pH data suggest that critically ill burn patients have gastric pH in excess of 4 a significant portion of the day. Thus, according to Tryba, the result of our study was "predictable." Since many similar studies, including ours and that of Fabian, report gastric pH to be elevated for a significant portion of the day in critically ill surgical patients not receiving AN, it would appear that the population at risk as defined by Tryba would be quite small. Nonetheless, these same patients have occasional measured gastric pH levels that are also quite low, indicating the requirement for some form of prophylaxis.

Our multivariant analysis indicated that injury severity and requirements for intubation but not stress ulcer prophylaxis regimens were related to the development of nosocomial pneumonia. Inhalation injury was not specifically related to the development of pneumonia, presumably because intubation, an event that is required in approximately 90% of inhalation injury patients, is more strongly associated with the development of pneumonia. This refines the predictive value of inhalation injury alone since only the most severly injured patients require intubation. Fabian et al. reported similar findings, indicating that in trauma patients injury severity, including measures of CNS injury but not stress ulcer prophylaxis regimens, were directly related to nosocomial pneumonia rates.[30] Our finding of a significant increase in the incidence of pneumonia in patients while intubated in the sucralfate group reflects a limitation of univariate analysis in assessing the importance of risk factors associated with the development of pneumonia. When we utilized multivariate analysis, sucralfate therapy was not associated with an increased risk of pneumonia, possibly indicating that the intubation cohorts were not as evenly matched as univariate analysis indicated. This is further supported by comparison of the severity indices, which indicated that the sucralfate group tended to be somewhat more severely injured than the acid neutralizing group. The frequency of pneumonia as a serious comorbid factor in patients with burns and those with other injuries justifies careful study of therapies that may decrease the incidence of this life-threatening complication. Our data and a review of other well designed trials involving trauma patients indicate that there is no benefit from the use of non-acid neutralizing prophylaxis in the prevention of gastric stress ulcerations and subsequent nosocomial pneumonia.[30,31] The occurrence of clinically significant upper gastrointestinal bleeding in three patients in the sucralfate group, in one of whom surgical control was required, is alarming even though the small number of study patients prevented such from attaining statistical significance. That failure rate in combination with lack of prophylactic regimen effect on the incidence of pneumonia speaks for our continued preference for acid neutralizing regimens of upper gastrointestinal stress ulcer prophylaxis.

REFERENCES

1. Czaja AJ, McAlhany JC, Pruitt BA Jr: Acute gastroduodenal disease after thermal injury: An endoscopic evaluation of incidence of natural history. *N Engl J Med* 291:925, 1974
2. Knight A, Bihari D, Tinberg J: Stress ulceration in the critically ill patient. *Br J Hosp Med* 20:216, 1985
3. Sat N, Kawano S, Kamada T, et al: Hemodynamics of the gastric mucosa and gastric ulceration in rats and in patients with gastric ulcer. *Dig Dis Sci* 31:35S, 1986
4. McAlhany JC, Czaja AJ, Pruitt BA: Antacid control of complications from acute gastroduodenal disease after burns. *J Trauma* 16:645, 1976
5. Zinner MJ, Zuidema GD, Smith PL, et al: The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. *Surg Gynecol Obstet* 153:214, 1981
6. Atherton ST, White DJ: Stomach as a source of bacteria colonizing respiratory tract during artificial ventilation. *Lancet* 2:968, 1978
7. Elpern EH, Jacobs ER, Bone RC: Incidence of aspiration in tracheally intubated adults. *Heart Lung* 16:527, 1987
8. Drika MR, Craven DE, Celli BR, et al: Nosocomial pneumonia in

intubated patients randomized to sur ste versus antacids and/or histamine type 2 blockers: The re gastric colonization. *N Engl J Med* 317:1376, 1987
9. Tryba M: Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: Sucralfate vs antacids. *Am J Med* 83 (*Suppl* 3B):117, 1987
10. Weinstein RA: Failure of infection control in intensive care units: Can sucralfate improve the situation? *Am J Med* 91 (*Suppl* 2A):132S, 1991
11. Kappstein I, Schulgen G, Friedrich T, et al: Incidence of pneumonia in mechanically ventilated patients treated with sucralfate or cimetidine as prophylaxis for stress bleeding: Bacterial colonization of the stomach. *Am J Med* 91 (*Suppl* 2A):125S, 1991
12. Cioffi WG, Kim SH, Pruitt BA Jr: Cause of mortality in thermally injured patients. In Lorenz S, Zellner P-R (eds): *Die Infektion Beim Brandverletzten*, Proceedings of the "Infektionsprophylaxe und Infectionsbekämpfung beim Brandverletzten" International Symposium. Darmstadt, Germany, Dr. Dietrich Steinkopff Verlag, 1993, pp 7–11
13. Shirani KZ, Pruitt BA Jr, Mason AD: The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg* 205:82, 1987
14. Tryba M: The gastropulmonary route of infection—Fact or fiction? *Am J Med* 91 (*Suppl* 2A):135S, 1991
15. McManus WF, Vaughan GM, Becker WK, et al: Clinical operation, Center for Treatment of Burned Soldiers. In Pruitt BA (ed): *The U.S. Army Institute of Surgical Research Annual Research Progress Report for Fiscal Year 1991, San Antonio.* Washington, D.C., U.S. Government Printing Office, 1992, pp 1–33
16. Lagner AN, Lenz K, Base W, et al: Prevention of upper gastrointestinal bleeding in long-term ventilated patients. *Am J Med* 86 (*Suppl* 6A):81, 1989
17. MacLean LD: Prophylactic treatment of stress ulcers: First do no harm. *Can J Surg* 31:76, 1988
18. Tryba M: Side effects of stress bleeding prophylaxis. *Am J Med* 86 (*Suppl* 6A):85, 1989
19. Wilcox CM, Spenney JG: Stress ulcer prophylaxis in medical patients: Who, what, and how much. *Am J Gastroenterol* 83:1199, 1988
20. Reines HD. Do we need stress ulcer prophylaxis? *Crit Care Med* 18:344, 1990
21. Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: A reappraisal. *Ann Intern Med* 106:562, 1987
22. Cook DJ, Witt LG, Cook RJ, et al: Stress ulcer prophylaxis in the critically ill: A meta-analysis. *Am J Med* 91:519, 1991
23. Reusser P, Zimmerli W, Scheidegger D, et al: Roloe of gastric colonization in nosocomial infections and endotoxemia: A prospective study in neurosurgical patients on mechanical ventilation. *J Infect Dis* 160:414, 1989
24. Martinez-Pellus AE, Ruiz J, Garcia J, et al: Role of selective digestive decontamination (SDD) in the prevention of nosocomial pneumonia (NP): Is gastric decontamination necessary? *Intens Care Med* 18:218, 1992
25. Samloff IM, O'Dell C: Inhibition of peptic activity by sucralfate. *Am J Med* 79 (*Suppl* 2C):15, 1985
26. Rees WDW: Mechanisms of gastroduodenal protection by sucralfate. *Am J Med* 91 (*Suppl* 2A):59S, 1991
27. Eddleston JM, Vohra A, Scott P, et al: A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients. *Crit Care Med* 19:1491, 1991
28. Cook DJ, Laine LA, Guyatt GH, et al: Nosocomial pneumonia and the role of gastric pH: A meta-analysis. *Chest* 100:7, 1991
29. Tryba M: Sucralfate versus antacids or H2-antagonists for stress ulcer prophylaxis: A meta-analysis on efficacy and pneumonia rate. *Crit Care Med* 19:942, 1991
30. Fabian TC, Boucher BA, Croce MA, et al: Pneumonia and stress ulceration in severely injured patients. *Arch Surg* 128:185, 1993
31. Simms H, DeMaria E, McDonald L, et al: Role of gastric colonization in the development of pneumonia in critically ill trauma patients: Results of a prospective randomized trial. *J Trauma* 31:531, 1991
32. Moore FA, Moore EE, Jones TN, et al: TEN versus TPN following major abdominal trauma: Reduced septic morbidity. *J Trauma* 29:916, 1989
33. Kudsk KA, Croce MA, Fabian TC, et al: Enteral vs parenteral feeding: Effects or ntic morbidity following blunt and penetrating trauma. *Ar rg* 215:503, 1992
34. Tryba M: Pneumonia due to stress ulcer prophylaxis with cimetidine: A necessary consequence? *Arch Surg* 128:1078, 1993

DISCUSSION

Dr. Philip S. Barie (New York, New York): This study was generally well designed, well performed, and very well presented. The authors are to be commended.

The authors have shown no difference between aluminum sucrose octosulfate (sucralfate) and pH control with combined antacid and H_2-antagonist receptor therapy on the incidence of pneumonia. Notably, they have done so in a relatively homogeneous patient population and in a group of patients at theoretically very high risk of pneumonia in that more than one half of their evaluable patients had inhalation injury. This paper presents, in my view, the highest risk group of patients in which such a study has been done.

Although post-hoc subgroup analysis revealed some differences, most notably a significantly higher rate of pneumonia in intubated patients who received sucralfate, I believe the take-home message is that prophylaxis for stress gastritis does not impact the pneumonia rate. As Doctor Cioffi has pointed out, his sucralfate patients were probably a bit sicker. Most studies of this type do not show a trend toward higher pneumonia rates with sucralfate therapy. Alarmingly, the authors noted three patients with serious bleeds in the sucralfate group, one of whom required gastrectomy. This conforms to our own casual observations.

I would like to place the paper in perspective with respect to its two primary design limitations: number one, that antacids and H_2 blockers were given together rather than separately, and number two, that the diagnosis of pneumonia on standard clinical grounds leaves much to be desired. [Slide] This is a summary of the two meta-analyses, both published within months of each other in 1989, which led to this whole debate.

The first was in *Critical Care Medicine*, in aggregate looking at about 12 studies. This paper had a major methodologic flaw in that data from three abstracts without peer review of any type were included in the meta-analysis.

The second paper, published in *Chest*, was more forthright in its analysis of the data that were included. Without going into the methodologic limitations of meta-analysis, some of which are quite exciting, only eight of 48 of these stress ulcer prophylaxis papers talked about pneumonia. The papers included were of widely disparate qualities, studied selected rather than randomized patients in three of the eight reports with randomized studies, and in none was there blinding of either the radiologist or the treating clinician as to the status of pneumonia. Interestingly, they found that antacid prophylaxis, contrary to belief at the time, did not increase the incidence of pneumonia.

This study has been done in a homogeneous patient population, which I think is one of the major strengths of the study. This literature in general has suffered from the fact that these studies have been done in a widely disparate patient populations. The diagnostic criteria for pneumonia have been a major problem. And, of course, the presence of not only an endotracheal tube but a nasogastric tube may confound the results.

One potentially important aspect that has not really been discussed is what happens when sucralfate itself is aspirated. [Slide] This is a study from the anesthesia group at Harvard in which they used three groups of rats, and put sucralfate or saline into a fresh tracheostomy. The sucralfate was buffered to two different pH levels. They found evidence of a fairly severe pulmonary parenchymal injury, so sucralfate into the lungs appears not to be benign, either.

[Slide] Nosocomial pneumonia is a difficult diagnosis to

make. This is one of the limitations of virtually all of these studies, in that clinical criteria are used while the state of the art, at least for pneumonia research, has progressed.

This paper appeared in *Chest* in 1993. It is from a Belgian group that is one of the leaders in clinical research in nosocomial pneumonia, particularly using the protected specimen brush catheter. They did a prospective study of 84 patients and asked themselves how good they were at determining whether patients had pneumonia. In fact, they were accurate only 62% of the time when compared with predefined rigid criteria. The residents were as accurate as the staff physicians, and unanimous assessments were incorrect 10% of the time. Thus, even for experienced physicians, nosocomial pneumonia is a difficult diagnosis to make.

[Slide] Putting Doctor Cioffi's data, as well as the results of two other recent surgical studies performed by our colleagues Doctor Simms and Doctor Fabian, in perspective, you can see that the incidence of pneumonia is the same for sucralfate versus pH control (30% vs. 27%). If these studies are added to the previous meta-analyses the argument that sucralfate lowers the nosocomial pneumonia rate essentially evaporates.

I would like to ask Doctor Cioffi three questions. Number one, did you control or look at pH in your sucralfate group? Sucralfate has been reported to be a weak agonist of duodenal bicarbonate secretion. Number two, do you believe the lingering perception in the literature that antacids and H_2 blockers may pose different risks? Also, in the future would you consider making some attempt to quantitate nosocomial pneumonia using such techniques as the protected specimen brush or bronchoalveolar lavage? Thank you.

Dr. William G. Cioffi (Closing): Thanks, Doctor Barie, for your discussion. We did measure gastric pH in both of our groups. We recorded for all 96 evaluable patients the highest and lowest pHs of the day and we also recorded hourly pH data on a smaller subgroup of the patients.

In terms of the smaller subgroup, we found that in the sucralfate group only 38% of the time was the pH less than 4 despite the lack of acid neutralization, whereas that was true 18% or 19% of the time in the acid neutralization group. In terms of the patients as an aggregate, the low pH in the sucralfate group averaged approximately 3.3 and the high just over 5. In the acid neutralization group the lowest pH averaged just under 4 and the high near 6.

So it was apparent to us that despite the lack of acid neutralization therapy administered by us that critically ill burn patients spent a considerable portion of their day with their gastric pH above 4. That is potentially the explanation for why our colonization rates were similar.

Why did we use antacids and H_2 blockers together? That has been our standard therapy for more than a decade and has led to our clinical success in eradicating stress ulcers as a complication in burn patients. Thus we wanted to study what we do clinically in our patients with what was in the literature.

In terms of antacids having been implicated both in Doctor Fabian's and in Doctor Tryba's papers as being responsible for the increased incidence of pneumonia because of the volume of antacids required to increase gastric pH, I think our data put that issue to rest.

And finally, pertaining to the diagnosis of pneumonia, we struggle, like all ICUs, in finding the right way to make the diagnosis. We have tried various other methods, but unlike our European colleagues we have not found any benefit of protected brush specimens or BAL or anything else, in terms of being that much better.

clinical investigations

Nosocomial Pneumonia and the Role of Gastric pH*

A Meta-Analysis

Deborah J. Cook, M.D.;† Loren A. Laine, M.D.;‡
Gordon H. Guyatt, M.D., F.C.C.P.;† Thomas A. Raffin, M.D., F.C.C.P.§

Purpose: To examine the differential effect of drugs used for stress ulcer prophylaxis on nosocomial pneumonia in critically ill patients.
Data Identification: Computerized bibliographic search of published and unpublished research.
Study Selection: Independent review of 48 randomized controlled trials of prophylaxis identified eight relevant studies.
Data abstraction: The population, intervention, and outcomes were evaluated by duplicate independent review.
Results: The incidence of pneumonia was lower in critically ill patients receiving antacids and/or histamine-2-receptor antagonists as compared with patients receiving no stress ulcer prophylaxis (common odds ratio 0.42, 95 percent CI 0.17 to 1.11). When stress ulcer prophylactic therapy was titrated to achieve a gastric pH of 3.5 or greater, there was a trend favoring a decreased incidence of pneumonia (0.66, 95 percent CI 0.24 to 1.78). In trials comparing sucralfate with pH-altering drugs, the common odds ratio of 0.55 (0.28 to 1.06) suggests a 45 percent risk reduction with the use of sucralfate.
Conclusion: Stress ulcer prophylaxis with drugs which raise gastric pH does not increase the incidence of pneumonia in comparison to placebo or control therapy. The use of sucralfate is associated with a lower incidence of nosocomial pneumonia in comparison to agents which raise gastric pH. However, methodologic deficiencies, small sample sizes, and the failure to examine the effects of antacids and histamine-2-receptor antagonists separately make a large prospective randomized trial necessary to confirm or refute these findings. *(Chest 1991; 100:7-13)*

Nosocomial pneumonia occurs in 0.5 to 5.0 percent of all hospital admissions.[1] The incidence in mechanically ventilated patients is 4 to 21 times higher than in patients not requiring assisted ventilation.[2-4] Pneumonia remains the leading cause of death from nosocomial infection,[5,6] responsible for 15 percent of hospital deaths;[1] the associated mortality rate in ventilated patients approaches 50 to 60 percent.[5-8]

Colonization of the upper respiratory tract with Gram-negative bacteria is a major risk factor for the development of nosocomial pneumonia.[9,10] Factors believed to predispose to colonization include lung disease, endotracheal intubation, diabetes, malnutrition, antibiotic therapy, and gastric acid neutralization.[10]

Acid pH maintains the sterility of the stomach in the fasting state. However, in critically ill patients receiving stress ulcer prophylaxis with drugs which suppress (histamine-2-receptor antagonists) or neutralize (antacids) gastric acid, growth of intragastric Gram-negative bacteria is common.[11-14] Transmission of these organisms from the stomach to the respiratory tract has been well documented.[12,13,15-17] Therefore, in patients receiving stress ulcer prophylaxis, the stomach is a potential reservoir of pathogenic bacteria that may colonize the lower respiratory tract. Aspiration of these organisms is believed to be an important mechanism in the development of nosocomial pneumonia. Furthermore, the presence of an endotracheal tube does not afford complete protection; the rate of passive aspiration may be as high as 20 percent.[18]

The role of gastric colonization in the development of pulmonary infection is supported by a prospective study of risk factors for pneumonia in ventilated patients,[6] which showed that gastrointestinal bleeding prophylaxis using histamine-2-receptor antagonists with or without antacids was independently associated with the development of pneumonia. In another series of ventilated patients receiving stress ulcer prophylaxis with pH-altering drugs, the rate of pneumonia directly correlated with increasing gastric pH ($p<0.025$); the incidence of pneumonia was 41 percent in patients

*From the †Departments of Medicine and Epidemiology and Biostatistics, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada; ‡the Department of Medicine, USC School of Medicine, Los Angeles; and §the Department of Medicine, Division of Respirology, Stanford University Medical Center, Stanford, CA.
Dr Cook is Research Scholar, St. Joseph's Hospital Foundation, Hamilton, Canada.
Manuscript received August 20; revision accepted November 26.
Reprint requests: Dr. Cook, Epidemiology and Biostatistics, McMaster University Medical Center, Hamilton, Ontario, Canada L8N 3Z5

whose gastric pH was less than 3.4, whereas the rate was 69 percent in patients whose pH was greater than 5.0.[13] This, however, could reflect the fact that the more severely ill patients were the ones receiving prophylaxis. Moreover, many critically ill patients have an increased gastric pH without prophylactic therapy. This study was limited in that its design was uncontrolled, and its small sample size was associated with wide confidence intervals.

Nevertheless, the efficacy of stress ulcer prophylaxis in preventing gastrointestinal bleeding in the critically ill has prompted widespread use of drugs which suppress or neutralize gastric pH in the intensive care unit setting.[14] In addition, sucralfate, an agent which has cytoprotective properties but does not appreciably increase pH, is also efficacious in the prevention of bleeding due to stress ulceration.[19-22]

A number of randomized controlled trials have been performed which examine the extent to which various prophylactic agents are associated with nosocomial pneumonia. Although some of these studies have been reviewed recently,[10,23] no attempt has been made to synthesize these data in a formal quantitative manner. We, therefore, performed a meta-analysis of the results of eight randomized clinical trials of gastrointestinal bleeding prophylaxis to evaluate the differential effect of preventive agents on the rate of nosocomial pneumonia.

Methods

Locating Research

MEDLINE and EMBASE (Excerpta Medica online) was searched from 1966 onwards, to locate research published by January 1, 1990, in the area of nosocomial pneumonia and the role of gastric pH. MeSH terms used for key and text word searching included pneumonia, critical care, hemorrhage (gastrointestinal), and clinical trials. Frequently cited references were identified and SCISEARCH (Science Citation Index online) was used to locate additional studies that cited these articles. Reference lists of all articles obtained were scanned to identify additional research not found in the computerized bibliographic database searching.

Strategies to obtain unpublished material included searching *Federal Research in Progress, Foundations, Medical Research Directory, IEP, NTIS, Microlog, Conference Papers Index* and *Biosis Previews*. A comprehensive list of relevant articles was constructed; authors of the primary studies selected were consulted to review this list and provide information on further published or unpublished material. The National Institutes of Health and Medical Research Council of Canada were also contacted to identify research projects previously or presently funded by these institutions. Finally, pharmaceutical companies marketing drugs used for gastrointestinal bleeding prophylaxis (cimetidine, ranitidine, famotidine, Mylanta, Maalox, alternagel, sucralfate, misoprostil and enprostil) were contacted by letter to identify industry research presently or previously ongoing in the area of stress ulcer prophylaxis and nosocomial pneumonia. All responses were followed up through contact with the identified investigators.

Selecting Research

In screening for eligible articles for the overview, these three criteria were applied in duplicate, independently by two of us (DJC and LAL) to the titles and abstracts of each reference in the literature search:

(1) design criterion: randomized clinical trials comparing one or

Table 1—*Criteria for Assessment of Methodologic Quality

I. Population
  (a) Patient selection:
    2: Consecutive eligible consenting patients/random series
    1: Attempt made to enroll as such, with failure due to reasons outlined explicitly
    0: Selected patients (not consecutive or random)/not described
  (b) Patient characteristics: state: Y/N
    Age (mean differs by <10%)
    Sex (proportion of males in each group differs by <10%)
    APACHE/TISS/ISS/GRS Score (mean differs by <10%)
    Diagnoses (proportion with the following differing by <10%)
      Chronic obstructive airways disease
      Respiratory failure (mechanical ventilation)
      Pneumonia at entry
      Tracheostomy
      Sepsis
      Renal failure
      CNS disease
      Trauma
      Coagulopathy
      Hepatic failure
      Burns
      Major surgery
      Peptic ulcer disease, GI surgery
      Diabetes/alcoholism

To score:
  2: groups comparable on 6 or more characteristics
  1: groups comparable on 3-5 characteristics
  0: groups comparable on 2 or fewer characteristics

II. Intervention
  (a) Randomization:
    2: Nonmanipulable (call to data coordinating centre, masked drug packages)
    1: Potentially manipulable (sealed envelope, computer generated random number table), OR randomization stated with no further information
    0: Quasirandomization (hospital ID, date)
  (b) Blinding:
    2: Blinding of radiologists to treatment group and blinding of physicians to clinical endpoints
    1: Blinding in only one of the above instances
    0: Potentially unblinded, unblinded, or can't tell

III. Outcome
  (a) Definition of pneumonia:
    2: Probable pneumonia:
      Roentgenographic criterion and at least three other criteria (*ie*, fever, leukocytosis, purulent sputum, isolation of pathogenic bacteria from sputum or blood, or decreased alveolar-arterial oxygenation difference)
    1: Possible pneumonia:
      Roentgenographic criterion and at least one other criterion
    0: Doubtful pneumonia:
      Inadequate description/single criterion

*The foregoing criteria were used to evaluate the methodology of each trial. The numbers 2, 1 and 0 are the scores corresponding to the methodologic criterion satisfied in each study.

ore prophylactic drugs with each other, or with a placebo or ntrol group.
rget population: critically ill patients.
itcome measure: nosocomial pneumonia.
icles identified by one or both authors were retrieved. equently, these same criteria were again applied independently e full text of the articles which met the first eligibility screening der to make a final selection of articles.

ssment of Methodologic Quality

riteria used to assess the methodologic quality of the primary lies are found in Table 1. Each study was evaluated indepen- tly based on specification of the population, intervention and come.

ta Collection

Duplicate independent data extraction was performed by two of (DJC and LAL). Missing data were solicited from authors of the imary research and abstracted data were checked in the following anner: the corresponding author of each article received a letter id copy of the completed data abstraction forms. He or she was en requested to correct erroneous assessments and provide issing information where necessary. Authors of articles published n abstract form were contacted to request full manuscripts and ata sets.

)ata Analysis

Agreement between coders for research selection and validity assessment was measured by kappa with quadratic weights. Disagreement was resolved by consensus. The measure of association used in this meta-analysis is the odds ratio. The Breslow-Day method was used to test for homogeneity under the null hypothesis that the odds ratios are the same across studies. The corrected Mantel-Haenszel chi square test (two-tailed) was used to test for association between exposure and outcome. The Mantel-Haenszel technique was also employed to estimate the common odds ratio for all studies; the 95 percent confidence interval was calculated using the Cornfield method.

Prior Hypotheses Regarding Sources of Heterogeneity

When conducting a meta-analysis, heterogeneity (that is, major differences in the apparent effect of the interventions across studies) is often found. When heterogeneity is present, it must be explained. Thus, before analyzing the results of this overview, we developed two hypotheses concerning underlying differences in the studies which might explain heterogeneity of the study results, if indeed significant heterogeneity was found.

First, we speculated that titration of prophylactic therapy to achieve a specific gastric pH alters the incidence of nosocomial pneumonia. The biologic rationale for this hypothesis was that trials not titrating therapy to gastric pH might fail to raise pH to levels which would increase the risk of pneumonia, whereas trials that titrated therapy to specific pH *would* do so. The second hypothesis to explain heterogeneity was that sucralfate differs from pH-altering drugs in its effect on the incidence of pneumonia. The biologic rationale for the second hypothesis was that sucralfate has been shown to have bacteriostatic properties which would be absent in studies using placebo or no-treatment control subjects.[13]

Results

Forty-eight randomized trials were identified which compared stress ulcer prophylactic agents with each other or control groups in critically ill patients. Only ten studies involving 1,198 patients met the first eligibility screening.[24-34] One trial,[29] which evaluated bronchial secretions and blood cultures in only a proportion of the total number of patients, also had an inadequate definition of nosocomial pneumonia and was subsequently excluded. A second trial compared

Table 2—*Randomized Controlled Trials of Stress Ulcer Prophylaxis and Nosocomial Pneumonia*

Study, yr	Driks et al, 1987[26]	Tryba 1987[25]	Reusser et al, 1989[31]	Karlstadt et al, 1989[27]	Laggner et al, 1989[32]	Karlstadt et al, 1990[28]	Ryan et al, 1990[34]	Karlstadt et al, 1990[33]
No. Patients & Type of ICU	69 Medical/ Surgical	100 Medical/ Surgical	40 Surgical	104 Medical/ Surgical	32 Medical/ Surgical	87 Medical/ Surgical	90 Medical/ Surgical	13 Medical/ Surgical
Proportion Ventilated	1.0	1.0	1.0	0.44	1.0	0.21	1.0	. . .
Treatment	1 g sucralfate q6h NG	1 g sucralfate q4h NG	150-200 mg IV ranitidine ± antacids to achieve pH >4.0	300 mg cimetidine then 50 g/h	50 mg ranitidine q4H IV to achieve pH >3.5	300 mg cimetidine then 50 mg/h	cimetidine 900 mg/d	300 mg cimetidine then 50-100 mg/h
	vs	vs	vs	vs	vs	vs	vs	vs
	Standard regimens of antacid & histamine receptor antagonists sometimes titrated to pH	10 ml antacid q2h NG	Control	Placebo	Sucralfate 1 g NG q4h	Placebo	Sucralfate 1 g q6h	Placebo
Methodologic Quality Score	7	5	5	7	6	5	3	2

ranitidine with pirenzipine.[24] The latter is an anticholinergic agent with relatively specific action on gastric secretion through muscarinic receptor blockade. Although a methodologically sound study, this trial was also excluded from the analysis because pirenzipine is not approved or used for stress ulcer prophylaxis in North America. Four of the eight remaining studies were published in peer-reviewed journals;[26,28,30-32] one of those published in peer-reviewed journals was reported in two parts.[30,31] Of the other four trials, one[25] was presented in a symposium. The remaining three studies were published in abstract form;[27,33,34] data sets were made available to the authors in one case (R. Karlstadt, personal communication, 1989).

Agreement between reviewers for the selection of relevant articles was 100 percent. Chance-corrected agreement for the validity assessment showed kappa scores of 0.82 to 0.93. Causes of disagreement were errors of oversight as often as differences in opinion.

One trial compared antacids and/or histamine-2-receptor antagonists with sucralfate,[26] one compared antacids and sucralfate,[25] one compared ranitidine with sucralfate,[32] three compared cimetidine with placebo,[27,28,33] one compared cimetidine with sucralfate,[34] and one compared ranitidine and antacids with placebo.[30,31] A brief description of the studies is given in Table 2. A variety of patients with different diagnoses were studied, including neurosurgery patients[30,31] and a mixed medical and surgical population.[25-28,32-34] The mortality rates ranged from 2 to 50 percent across studies.

To examine the role of gastric pH in the development of nosocomial pneumonia, we evaluated trial results according to whether or not treatment altered gastric pH. Patients receiving histamine receptor antagonists or antacids showed a trend toward an increased incidence of pneumonia in three trials,[26,28,32] and a significantly greater incidence in the fourth study.[25] The remaining trials showed a trend toward[30,31,33,34] and significant decrease[27] in the rate of pneumonia with pH-altering drugs. The statistical test for homogeneity suggested that there were systematic differences between results of these six studies that would bring into question the validity of aggregating data ($p = 0.04$); therefore, the results of these eight trials were not combined.

Having found heterogeneity of results, we then examined the following two *a priori* hypotheses to explain this heterogeneity.

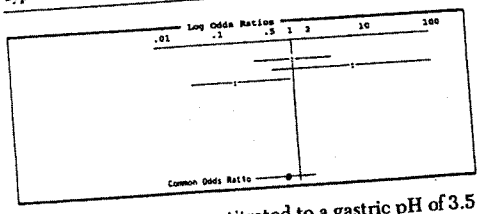
(1) Titration of prophylactic therapy to achieve a specific gastric pH alters the incidence of nosocomial pneumonia.

(2) Sucralfate differs from pH-altering drugs in its effect on the incidence of pneumonia.

To test the first hypothesis, a sensitivity analysis was performed examining only the three trials in which

Table 3—*Prophylax... itrated to Gastric pH vs No Titration*

Author, Year	Exper Obs	Exper Tot	Control Obs	Control Tot	Odds Ratio	95% CI Lo	95% CI Hi
Reusser et al, 1989[31]	7	19	8	21	0.95	0.27	3.37
Lagner et al, 1989[32]	2	16	0	16	7.90	0.47	99.99
Karlstadt et al, 1989[27]	0	45	6	49	0.13	0.03	0.69
Typical odds ratio and 95% CI					0.63	0.24	1.62



pH-altering therapy was titrated to a gastric pH of 3.5 or greater.[27,30-32] The statistical test for homogeneity indicated that the differences between odds ratios in the three different studies were consistent with random variation alone ($p = 0.21$), suggesting the appropriateness of combining the studies to yield a single typical common odds ratio. The individual odds ratios and common odds ratio of 0.66 (95 percent confidence interval 0.24 to 1.78) are displayed in Table 3. The confidence interval crosses the odds ratio of unity (which corresponds to no beneficial or adverse treatment effect). Thus, there is no significant effect on the rate of pneumonia in patients receiving prophylactic therapy titrated to gastric pH of 3.5 or greater. It should be noted, however, that the extent to which a pH of 3.5 continuously is achieved is uncertain. Gastric pH was significantly higher in the cimetidine group than the placebo group in one trial,[30,31] signifi-

Table 4—*pH-Altering Drugs vs Placebo/Control*

Author, Year	Exper Obs	Exper Tot	Control Obs	Control Tot	Odds Ratio	95% CI Lo	95% CI Hi
Reusser et al, 1989[31]	7	19	8	21	0.95	0.27	3.37
Karlstadt et al, 1989[27]	0	45	6	49	0.13	0.03	0.68
Karlstadt et al, 1990[28]	1	54	0	33	5.01	0.09	99.99
Karlstadt et al, 1990[33]	0	56	4	61	0.12	0.00	1.92
Typical odds ratio and 95% CI					0.42	0.16	1.10

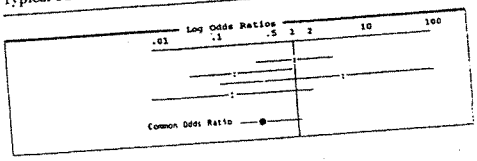
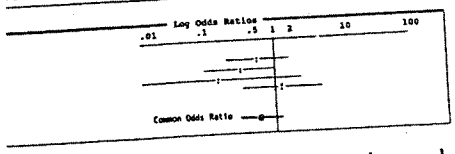


Table 5—*Sucralfate vs pH-Altering Drugs*

Author, Year	Exper Obs	Exper Tot	Control Obs	Control Tot	Odds Ratio	95% CI Lo	95% CI Hi
iks et al, 1987[28]	7	29	16	40	0.49	0.18	1.35
yba et al, 1987[25]	3	29	11	32	0.26	0.08	0.86
iggner et al, 1989[32]	0	16	2	16	0.13	0.01	2.12
yan et al, 1990[34]	8	45	6	45	1.41	0.39	5.13
ypical odds ratio and 95% CI					0.55	0.28	1.06



cantly higher in the ranitidine group than the sucralfate group in another,[32] but not explicitly reported in the third trial.[27]

To examine the second hypothesis, we first evaluated trials comparing drugs that alter gastric pH with placebo or control.[27,28,30,31,33] The statistical test for homogeneity again indicated that the differences between odds ratios in the four different studies were consistent with random variation alone ($p = 0.43$), as was the overall odds ratio examining the effect of altering pH ($p = 0.30$). The individual odds ratios and the common odds ratio of 0.42 (95 percent confidence interval 0.17 to 1.11) are displayed in Table 4. The odds ratio of unity is crossed by the confidence intervals of all three trials, as well as by the overall confidence interval. Although there is a trend toward a decreased rate of pneumonia in patients receiving pH-altering drugs, these results do not reach statistical significance.

Next, having established no significant difference in the incidence of pneumonia when comparing placebo/control with pH-altering drugs, trials comparing sucralfate with antacid and/or histamine-2-receptor antagonist therapy were evaluated[25,26,32,34] (Table 5). The test for homogeneity indicated that differences between odds ratios in the different studies were consistent with random variation ($p = 0.92$). The common odds ratio associated with the use of sucralfate was 0.55 (0.28-1.06), indicating a trend toward a reduced rate of pneumonia[35] with the prophylactic use of sucralfate as compared with pH-altering drugs.

Discussion

There is increasing agreement that scientific overviews which include a comprehensive search for relevant literature, an unbiased assessment of the validity of the primary research, and an examination of the reasons for differences in study results can provide important insights into both beneficial and adverse treatment effects.[35,36] Meta-analysis is a type of scientific overview which applies statistical principles to the quantitative results of study outcomes. This approach is used to combine the results of relevant trials, increase statistical power, and provide a more precise and robust estimate of treatment effect. The generally accepted methodologic criteria for meta-analysis[37,38] were met in this study. In particular, our literature search was extremely thorough and our selection criteria were well-defined. Although the quality assessment of the primary research was not performed by authors blinded to the study results, the risk of bias was reduced by explicit criteria for assessing methodologic quality, which resulted in high agreement between reviewers. The techniques of statistical analysis used were among those that have become standard for scientific overviews.[36-38]

Our sensitivity analyses examining differences between studies using a placebo or no-treatment control vs pH-altering drugs, and those comparing pH-altering agents with sucralfate, provided an explanation for the heterogeneity of study results found in the overall comparison of the eight trials comparing pH-altering drugs to all other regimens. A trend was found in favor of a reduced incidence of pneumonia with pH-altering drugs in comparison to placebo or no-treatment control. However, the comparison of pH-altering drugs to sucralfate revealed a trend toward a reduction in the incidence of nosocomial pneumonia in patients receiving sucralfate. Thus, the heterogeneity may be explained by the fact that the primary comparison involved a single analysis examining the effects of pH-altering drugs in comparison to one regimen which led to an equal or higher incidence of pneumonia, and one which led to an equal or lower incidence of pneumonia.

The effect of gastric volume on the incidence of nosocomial pneumonia must be considered because gastric volume is likely an important risk factor for aspiration. Sucralfate requires nasogastric instillation of approximately 30 ml every 6 h. Antacid therapy generally requires more frequent and often larger volume administration, while histamine-2-receptor antagonists decrease gastric secretion. Drugs which alter gastric pH should not necessarily be considered as equivalent therapies in clinical trials. Importantly, no study which compares sucralfate with histamine-2-receptor antagonists has shown a significant decrease in pneumonia for the sucralfate group. Therefore, differences between sucralfate and antacid therapy in two trials[25,26] might be explained by differences in gastric volume and/or the bacteriostatic effect of sucralfate on Gram negative organisms demonstrated *in vitro*.[13,35]

A limitation of this review is that only 8 of 48 trials evaluating stress ulcer prophylaxis either recorded or reported the outcome of nosocomial pneumonia. Thus, a publication bias may affect the results of this analysis. Examination of the methodologic quality of the individual trials (Table 2) reveals several other possible sources of bias. For example, although patient characteristics were similar between groups in the majority of cases, in three of the trials, the patients were selected.[25,27,32] It may be that characteristics which led patients to be selected in these trials are systematically related to the differential risk of pneumonia in patients treated with and without pH-altering agents. Moreover, confounding factors which could influence the incidence of pneumonia, such as diabetes, immunosuppression, and chronic endotracheal intubation, were not always described. Perhaps more plausibly related to outcome is the fact that, in diagnosing pneumonia, blinding of the radiologist and the clinician to the treatment group was not performed in any of the trials. This lack of blinding may result in considerable bias in these studies, given the difficulty in accurately diagnosing nosocomial pneumonia in critically ill patients.[39]

The proportion of patients included in this analysis with a nasogastric tube, an important risk factor for pulmonary infection,[10,40] is very high. In five studies,[25-28,34] all patients had nasogastric tubes inserted; in three studies,[30-33] the proportion is not specifically stated but it is likely close to 1.0. Because the proportion is so high in these studies, differences in the rate of nasogastric tube placement cannot explain differences in the rate of pneumonia. Although aspiration is infrequent when enteral feeding is administered through a small bore nasoenteral feeding tube,[41,42] nasogastric size was reported in only one trial.[25] The location of the tip of the feeding tubes was not recorded in any of the trials. Finally, enteral feeding, which increases intragastric volume, alters gastric pH[43,44] and increases isolation of gastric Gram-negative bacteria,[45] was not controlled in these studies.

The fact that only 8 of 48 randomized trials of gastrointestinal bleeding prophylaxis provided data on the incidence of pneumonia, and the methodologic deficiencies of these studies, limit the strength of the inferences that can be made from these data. Therefore, a large methodologically sound prospective randomized trial examining the different approaches to stress ulcer prophylaxis while controlling for confounding risk factors for nosocomial pneumonia, therefore, remains warranted.

References

1 Tobin MJ, Grenvik A. Nosocomial lung infection and its diagnosis. Crit Care Med 1984; 12:191-99

2 Celis R, Torres A, Gatell JM, Almella M, Rodriguez-Roisin R, Agusti-Vidal A. Nosocomial pneumonia: a multivariate analysis of risk and prognosis. Chest 1988; 93:318-24

3 Haley RW, Hooton TM, Culver DH, Stanley RC, Emori JG, Hardison CD, et al. Nosocomial infections in U.S. hospitals, 1975-1976: estimated frequency by selected characteristics of patients. Am J Med 1981; 70:947-59

4 Cross AS, Roup B. Role of respiratory assistance devices in endemic nosocomial pneumonia. Am J Med 1981; 70:681-85

5 Gross PA, Neu HC, Aswapokee P, Van Antwerpen C, Aswapokee N. Deaths from nosocomial infection: experience in a university hospital and a community hospital. Am J Med 1980; 68:219-23

6 Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1986; 133:792-96

7 Craven DE, Driks MR. Nosocomial pneumonia in the intubated patient. Semin Respir Infect. 1987; 2:20-33

8 Stevens RM, Teres D, Skillman JJ, Feingold DS. Pneumonia in an intensive care unit: a thirty month experience. Arch Intern Med 1974; 134:106-11

9 Johanson WG, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with Gram-negative bacilli: the significance of colonization of the respiratory tract. Ann Int Med 1972; 77:701-06

10 Niederman MS, Craven DE, Fein AM, Schultz DE. Pneumonia in the critically ill hospitalized patient. Chest 1990; 97:170-81

11 Ruddell WSJ, Axon ATR. Effect of cimetidine on the gastric bacterial flora. Lancet 1980; 672-74

12 du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonization of the airway. Lancet 1982; 242-45

13 Daschner F, Kappstein I, Engles I, Reuschenbach K, Pfisterer J, Kreig N, et al. Stress ulcer prophylaxis and ventilation pneumonia: prevention by antibacterial cytoprotective agents. Infect Control Hosp Epidemiol 1988; 9:59-65

14 Donowitz LG, Page MC, Mileur BL, Guenthner SH. Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. Infect Control 1986; 7:23-26

15 Atherton ST, White DJ. Stomach as a source of bacteria colonizing respiratory tract during artificial ventilation. Lancet 1978; 2:968-69

16 Kahn RJ, Serruys-Schoutens E, Brimioulle S, Vincent J-L. Influence of antacid treatment on the tracheal flora in mechanically ventilated patients (Abstract). Crit Care Med 1982; 10:229

17 Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalization on bacterial colonization in critically ill patients. Crit Care Med 1989; 17:211-16

18 Spray SB, Zuidema GD, Cameron JL. Aspiration pneumonia: incidence of aspiration with endotracheal tubes. Am J Surg 1976; 131:701-03

19 Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. Ann Int Med 1987; 106:562-67

20 Tryba M, Zevounou F, Toeroek M, Zenz M. Prevention of acute stress bleeding with sucralfate, antacids, or cimetidine: a controlled study with pirenzipine as a basic medication. Am J Med 1985; 79(suppl 2C):55-61

21 Borrero E, Bank S, Margolis I, Schulman ND, Chardavoyne R. Comparison of antacid and sucralfate in the prevention of gastrointestinal bleeding in patients who are critically ill. Am J Med 1985; 79(suppl 2C):62-64

22 Bresalier RS, Grendell JH, Cello JP, Meyer AA. Sucralfate suspension versus titrated antacid for the prevention of acute stress-related gastrointestinal hemorrhage in critically ill patients. Am J Med 1987; 83(suppl 3B):110-16

23 Wenzel RP. Hospital-acquired pneumonia: overview of the current state of the art for prevention and control. Eur J Clin

Microbiol Infect Dis 1989; 8:56-60
Tryba M, Zevonunou F, Wruck G. Stresblutungen und postoperative pneumonien bei intensivpatienten unter ranitidin oder pirenzepin. Dtsch Med Wschr 1988; 113:930-36
Tryba M. Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: sucralfate versus antacids. Am J Med 1987; 83(suppl 3B):117-24
Driks MR, Craven DE, Celli BR, Manning M, Burke RA, Garvin GM, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. N Engl J Med 1987; 317:1376-82
Karlstadt RG, Herson J, Palmer R, Frank W, Young M. Cimetidine reduces upper gastrointestinal bleeding and nosocomial pneumonia in intensive care unit patients (Abstract). Am J Gastroenterol 1989; 84:93
3 Karlstadt RG, Iberti TJ, Silverstein J, Lindenberg L, Bright-Asare P, Rockhold F, et al. Comparison of cimetidine and placebo for the prophylaxis of upper gastrointestinal bleeding due to stress-related gastric mucosal damage in the intensive care unit. J Intens Care Med 1990; 5:226-32
9 Laggner AN, Lenz K, Graninger W, Gremmel F, Grimm G, Base W, et al. Stresbluntungsprophylaxe auf einer internen intensivstation: sucralfat versus ranitidin. Anaesthesist 1988; 37:704-10
30 Reusser P, Gyr K, Scheidegger D, Buchmann B, Buser M, Zimmerli W. A randomized controlled endoscopic study of ranitidine and antacids for the prevention of gastroduodenal stress lesions and bleeding in critically ill patients (Abstract). Gastroenterology 1988; 94:373
31 Reusser P, Zimmerli W, Scheidegger D, Marbet GA, Buser M, Gyr K. Role of gastric colonization in nosocomial infections and endotoxemia: a prospective study in neurosurgical patients on mechanical ventilation. J Infect Dis 1989; 160:414-21
32 Laggner AN, Lenz K, Base W, Drume W, Schneeweiss B, Grimm G. Prevention of upper gastrointestinal bleeding in long term ventilated patients: sucralfate versus ranitidine. Am J Med 1989; 86(suppl 6A):81-84
33 Karlstadt R, D'Ambrosio C, McCafferty J, Palmer R, Rockhold F, Fox M. Cimetidine is effective prophylaxis against upper gastrointestinal bleeding in the intensive care unit. World Congress of Gastroenterology, Sydney, Australia, September 1990
34 Ryan P, Dawson J, Teres D, Navab F. Continuous infusion of cimetidine versus sucralfate: incidence of pneumonia and bleeding compared. Crit Care Med 1990; 18(suppl):253
35 Tryba M, Mantey-Stiers F. Antibacterial activity of sucralfate in human gastric juice. Am J Med 1987; 83(suppl 3B):125-27
36 Boissel JP, Blanchard J, Panak E, Peyrieux JC, Sacks H. Considerations for the meta-analysis of randomized clinical trials: controlled clinical trials. 1989; 10:254-81
37 Oxman AD, Guyatt GH. Guidelines for reading literature reviews. Can Med Assoc J 1988; 138:697-703
38 L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Int Med. 1987; 107:224-33
39 Andrews CP, Coalson JJ, Smith JD, Johanson WG Jr. Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest 1981; 80:254-58
40 Cheadle WG, Vitale GC, Mackie CR, Cuschieri A. Prophylactic postopertive nasogastric decompression. Ann Surg 1985; 202:361-65
41 Treolar DM, Stechmiller J. Pulmonary aspiration in tube-fed patients with artificial airways. Heart and Lung 1984; 13:667-71
42 Metheny NA, Eisenberg P, Spies M. Aspiration pneumonia in patients fed through nasoenteral tubes. Heart and Lung 1986; 15:256-61
43 Rigaud D, Chastre J, Accary JP, Bonfils S, Gibert C, Hance AJ. Intragastric pH profile during acute respiratory failure in patients with chronic obstructive pulmonary disease. Chest 1986; 90:58-62
44 Valentine RJ, Turner WW, Borman DR, Weigelt JA. Does nasoenteral feeding afford adequate gastroduodenal stress prophylaxis? Crit Care Med 1986; 14:599-601
45 Pingleton SK, Hinthorn D, Lui C. Enteral nutrition in patients receiving mechanical ventilation. Am J Med 1986; 80:827-32